Vol. 29 No. 147 October, 1954

ARCHIVES OF DISEASE IN CHILDHOOD

INCORPORATING THE BRITISH JOURNAL OF CHILDREN'S DISEASES

EDITORS
I. A. B. CATHIE and RICHARD H. DOBBS

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LONDON
BRITISH MEDICAL ASSOCIATION
TAVISTOCK SQUARE, W.C.1

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THE INFLUENCE OF SEVERE ILLNESS ON RICKETS*

BY

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(RECEIVED FOR PUBLICATION APRIL 1, 1954)

In my first lecture I discussed the effects of illness on the cells and cartilage of normal bone. Today I show their effects in rickets. First, what is the characteristic pattern in the bone in rickets uncomplicated by any other condition and is the response to severe illness different from that of normal bone? Next I shall take up the effects of illness on the calcium-phosphorus equilibrium in the blood, that is on rickets itself, since the changes in cartilage and bone depend directly on the changes in the tissue fluid and only indirectly on vitamin D deficiency. The effects on the cells in rickets pertain to growth, but those on the calcifying mechanism are at the heart of rickets itself. Is it by its effects there that illness precipitates rickets and once established, makes it worse, or in certain circumstances may it prevent its development altogether, or produce a partial or complete cure? There is evidence in favour of each view.

The Influence of Rickets on Growth

Cellular Pattern in the Shaft in Uncomplicated Rickets. Before discussing the effects of severe illness on the osteoblastic cells in rickets, we must know exactly what the cellular pattern is in its Simon purity. Fortunately, in Follis's and my series of children cases in which death had occurred suddenly or after short illnesses furnished the information. In brief the trabeculae were covered with thick cloaks of osteoblasts, many of which were enormous (Fig. 5, A and B). That they were in a state of increased activity, one could tell in occasional instances because the osteocytes in the osteoid were further separated by matrix substance than in the adjacent calcified bone laid down in the prerachitic period; in other words, the production of rachitic matrix substance had been excessive (Fig. 5C). Evidently in rickets in its purity the cellular proliferation and activity in the bone tend to be intensified rather than inhibited. In respect of the large numbers and large size of the osteoblasts the picture was comparable to that in the prematurely born infant.

An Explanation for the Great Activity of the Bone Cells. Schmorl (1909) furnished a teleological explanation for the increased thickness which the long bones sometimes develop in rickets and expressed the opinion that an excess of material was required to offset its poor quality. This may well be true, on account of the increased disposition of the bone to be compressed because of its lack of calcium salts, and as a result the cellular regulators, which are to be conceived of as continuously adjusting the bone mass to fit the requirements of stress and strain, must be kept in constant stimulation. In our view the regulating cellular mechanism for the cortex must reside in the periosteum and for the interior of the bone in the endosteal sheaths of the trabeculae and perhaps the osteocytes themselves.

Effect of Severe Illness on the Osteoblastic Cells. Skipping details, the effects are exactly the same in the rachitic as in the non-rachitic subject. The thick covering layers of huge cells vanish and in their places are scattered spindle cells, small osteoclasts, and the sparse flattened cells of the endosteal membrane. For a long time we were much puzzled by the contradiction of thick osteoid borders and a covering of cells too scant to have produced them (Fig. 5D). We finally realized that severe illness treated the rachitic bone exactly like the non-rachitic; the osteoid borders had been formed before the illness had produced its blighting effect and the scanty coverings of the trabeculae represented the atrophied remains of luxurious growths (Fig. 5E).

But it must not be concluded that the bone cells in severe rickets always responded in this way. Just as in some non-rachitic children the cells of the shaft seemed able to weather the storm, so in some cases of rickets osteoblastic proliferation and activity appeared unimpeded.

* The second of two inaugural Leonard Parsons Lectures delivered in Birmingham in 1953.

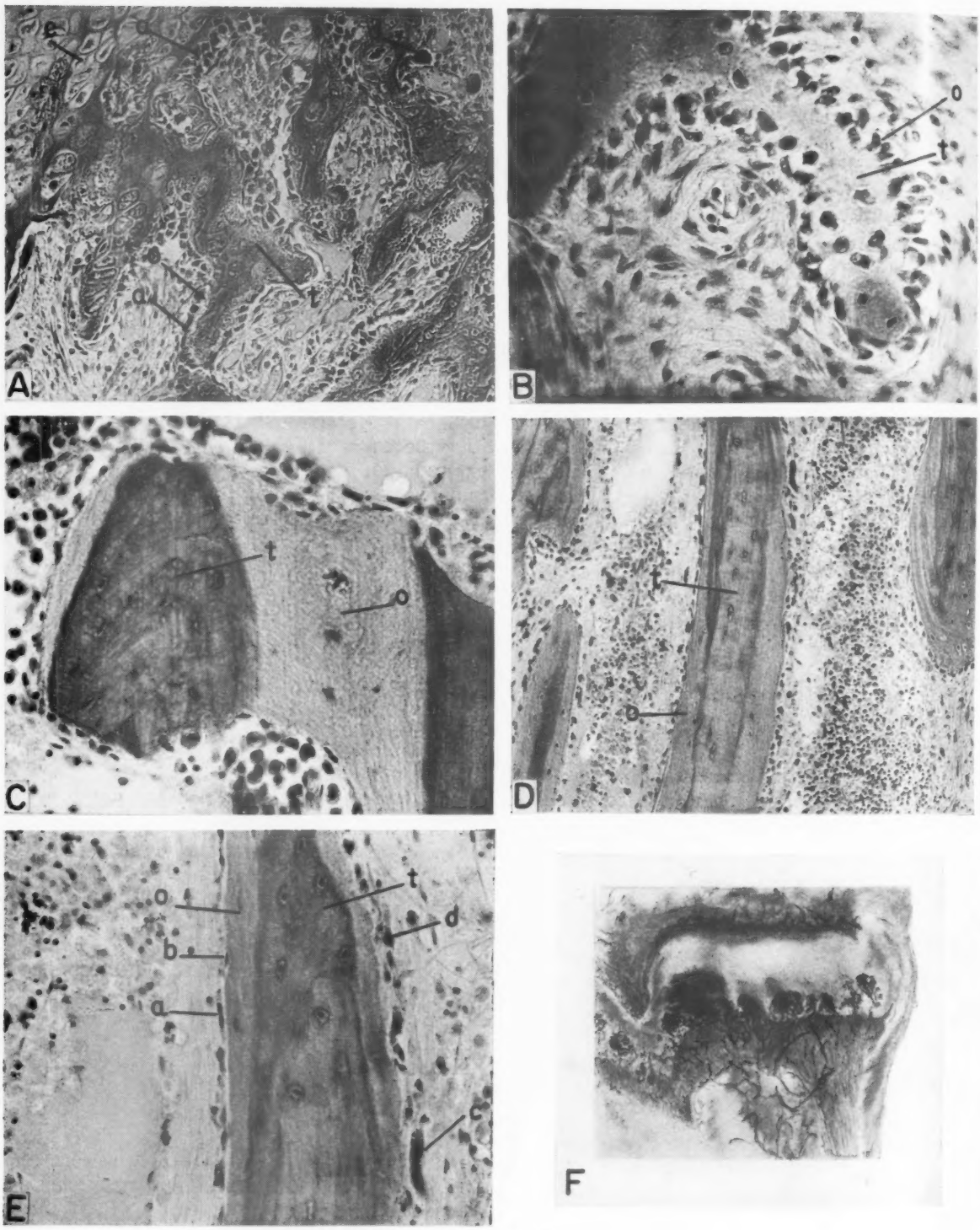

Fig. 5.

Dissociation of Cartilage Cell and Osteoblasts in Rickets. In the preceding lecture I pointed out the differences in behaviour of the cartilage cell and the osteoblast in normal bone under the same environment, which Follis and I have termed 'dissociation'. In rachitic children suffering from severe illness, we encountered this same dissociation, which appeared as in extreme manifestations of rickets in the cartilage and none (no osteoid) in the shaft. In 20 cases of moderate or severe rickets all the changes were cartilaginous; there was no osteoid. The absence of osteoid meant one of three possibilities: either it had never formed, or had disintegrated, or had become calcified and had disappeared by losing its identity. But this last possibility could be excluded because corresponding healing counterparts were absent in the cartilage. Of the alternatives left, the probable one was that the osteoid had not formed. That this was so was indicated in numerous cases in which well developed osteoid borders sheathed the trabeculae lower down in the section, the older ones, while there were none on the trabeculae near the cartilage, the most recently formed. This showed that the osteoblasts had ceased their building function which they had been able to exercise before. In the earlier part of our work we speculated that, since osteoid lacked impregnation with calcium salts, it might also lack stability and be subject to disintegration or transformation into connective tissue and disappear totally in that way. But further study convinced us that osteoid was destroyed exactly like calcified bone through dissolution by its surface cells and that, when this occurred, it was always focal so that patches of it were left, indicating that it had been present previously in larger amount. We gained the impression from our examinations of many examples of severe chronic rickets that osteoid must be as durable as calcified bone, for the broad osteoid borders were excellently preserved, though they must have been there for a long time. Progressing rickets in the cartilage and none in the shaft must be explained by dissociation, the cartilage cell able to multiply and the osteoblasts unable to secrete bone matrix.

Difficulty of Assessing Effects of Severe Illness on Cartilage. The changes caused by illness in the osteoblasts were as easy to recognize in the rachitic as in the non-rachitic subject, for in both the cells were in sharp relief along the trabecular edges. But the problem of distinguishing the effects on the solid mass of the rachitic cartilage, already thrown into the utmost confusion by the rickets itself, was too difficult for solution. In the non-rachitic bone the absence of the zone of empty or semi-empty capsules along the shaft border indicated that the maturation cycle of the cartilage cell had stopped, and reduction in width (actually length) of the epiphyseal plate served almost as a measure of the degree of growth inhibition, even to cessation itself. But these criteria were abolished by the rickets. Rickets interrupts the senescent cycle of the cartilage cell, as will be explained presently, so that criterion was excluded and the characteristic piling up of the cartilage in front of the shaft, which keeps increasing the longer the rickets lasts, makes any inferences from measurement impossible. In rickets artificially induced in the rat longitudinal growth diminishes progressively until it virtually stops and in the spontaneously developing rickets of the human being with its naturally occurring phosphorus deficiency, growth in length must become ultimately reduced, though important additional factors in the dwarfing process are the constant vitiation of gained length by crushing of the cartilage as fast as produced and also bending of the legs. But though common sense told us that rickets *per se* could not confer any immunity, i.e. illness must have the same inhibiting effect on rachitic as on normal cartilage, we were

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FIG. 5A.—28; × 90. Rib of 5-months-old child; sudden death, unexplained; rickets severe. The trabeculae (t) are covered with (a) osteoblasts, upper marked group cut tangentially; (o) osteoid; (c) rachitic cartilage; (d) osteoclasts.

FIG. 5B.—51; × 194. Rib of 8-months-old child, dying of heart failure in severe rickets. The proliferation of (o) osteoblasts is extremely marked and they are very large, comparable in that respect and also in number to the premature infant; (t) trabecula composed mostly of cartilage matrix.

FIG. 5C.—1118; × 194. Rib of 10-months-old child, dying of extensive tuberculosis; rickets ,chronic severe. The paucity of the cells in the (o) osteoid is well shown as compared by those in (t) calcified bone, the latter formed before the onset of the rickets. Also, the osteoid has only scattered covering of (b) osteoblasts in advanced regression.

FIG. 5D.—187; × 90. Rib of 12-months-old child dying of pneumococcal meningitis of four days' duration; rickets, chronic severe. (t) Calcified bone; (o) osteoid. Lining cells of osteoid in state of advanced regression, as shown in higher magnification, Fig. 5E.

FIG. 5E.—187; higher magnification, × 194, of preceding. (t) Calcified trabecula; (o) osteoid; (a) lining osteoblasts which appear to have fused; (b) single osteoblasts which appear to be destroying osteoid; (c) osteoclasts; (d) osteoclast and osteoblasts destroying osteoid. The breadth of the osteoid border means that, before the regressive changes started, they must have been covered with thick mantles of actively secreting osteoblasts. It is difficult to account for their disappearance.

FIG. 5F.—Drawing from the lower ulna in a case of severe rickets in which the blood vessels were injected with india ink. The injected blood vessels appear like bushes sticking out of the end of the shaft into the rachitic cartilage. The points explained in the text, namely, that the invasion occurs only here and there and that the blood vessels and osteoblasts may have to travel underneath the surface of the cartilage in order to find penetrable spots, are well illustrated.

totally unable to prove it. In the general confusion we could not establish that the proliferation rate was reduced or discover any structural counterpart to the growth retardation lattice. So, too, though we knew that the inactivation of the osteoblasts must have meant a diminished ability on the part of the shaft to invade the cartilage mass and reconstruct it into rachitic (osteoid) trabeculae, we could not find sure evidence that the process was interfered with. In severe chronic rickets the stasis and degenerative changes in the cartilage bordering on the shaft reach proportions which could scarcely be exceeded so that any additional interference would be masked by the general confusion. Our efforts, therefore, to establish growth disturbance in the cartilage when illness was superimposed on that inherent in the rickets itself failed completely.

Special Susceptibility of the Cartilage Cell. Rickets is characterized by deficiencies of phosphorus, calcium, or both in the tissue field, and the lesions in cartilage and bone depend directly on them and only indirectly on the vitamin D deficiency. A proof of this is the cure of the rickets by treatment with citrate, leaving the D deficiency unrelieved (Harrison and Harrison, 1941). In the defective medium of the tissue fluid the osteoblasts can flourish, proliferating profusely and producing bone matrix even in excess, as previously emphasized. But the cartilage cell in contrast is completely stymied, being rendered unable to complete the normal maturation cycle essential for the invasion of the capillaries and osteoblasts and reconstruction of the matrix frame into shaft. The defect, then, so far as the osteoblasts are concerned, is not in themselves but lies only in the failure of their product, the osteoid, to calcify, a failure obviously traceable to the subnormal calcium-phosphorus concentrations in the tissue fluid. But the defect, so far as the cartilage is concerned, is a biological block in the middle of its maturation performance.

The Development of the Endochondral Lesion. The inability of the cartilage cell to reach the endpoint in its cycle makes impossible its invasion by the capillaries and osteoblasts, and this is the primary and essential cause of the piling up of cartilage masses at the end of the shaft. The secondary cause, as now explained, is mechanical. In normal growth the cartilage cell columns can be imagined as standing on end, parallel to each other, and capping the shaft. Each column is completely embedded in homogeneous matrix substance. For an easier understanding, the cartilage cell columns may be compared to the honey and the surrounding matrix to the comb. The capillaries, surrounded by the osteoblasts, are attracted by the cartilage cells (the honey) and attack them in perfect order, abreast, in parallel vertical lines corresponding to the cartilage cell columns, a capillary for each column. They advance gradually up the columns by breaking into one cartilage cell capsule after another. Coincidentally the osteoblasts begin the manufacture of the future trabeculae by layering over with bone the paper-thin matrix walls of the holes caused by the destruction of the cartilage cells (the walls of the cells). Calcification occurs, not in the cartilage cells, but in the matrix walls, chiefly the vertical ones between the columns, and it is most important to realize that it always takes place in advance of the invading capillaries and osteoblasts. Thus in their progress into the cartilage these lie in a system of tiny tunnels, formed by the boring out, so to speak, of the cartilage cell columns, the walls of which have been given a metallic rigidity by the calcium salt deposition. It is the rigidity of the tunnel walls imparted by this inorganic reinforcement which ensures the orderly invasion. Here then is the point: when calcification of the cartilage stops, the tiny tunnels, incompletely reinforced by calcium salt deposition, become crushed and collapse from stress and strain causing 'roadblocks' over wide areas. The areas where these blocks occur are in the lines of stress, i.e. at those points where the trabecular pillars (the main trabecular complexes) on which the cartilage plate rests, abut. As the result then of the combined failure of the cartilage cell to complete its biological cycle and the development of these blocks, the capillaries and attendant osteoblasts are forced to find entrance into the cartilage where they can. They do this ultimately between the compression areas where the resistance is less, but may be obliged to travel some distance along the under surfaces of the cartilage in their search for penetrable spots. Through these they ultimately pass, finally working their way deep within in spite of the unready state of the cartilage cells, destroying the enveloping cells and converting their matrix into rachitic bone, i.e. osteoid trabeculae. In the course of this they grow into huge, bush-like structures (Fig. 5F). In this general way the endochondral lesion of rickets comes into being. As soon as the calcium and phosphorus are restored to the tissue fluids, the normal cartilage cell cycle reestablishes itself, calcium salts precipitate and endochondral ossification becomes normal again. Coincidentally, the osteoid in the shaft also calcifies.

The Effects of Severe Illness on Calcification. I have given this detailed explanation of the genesis

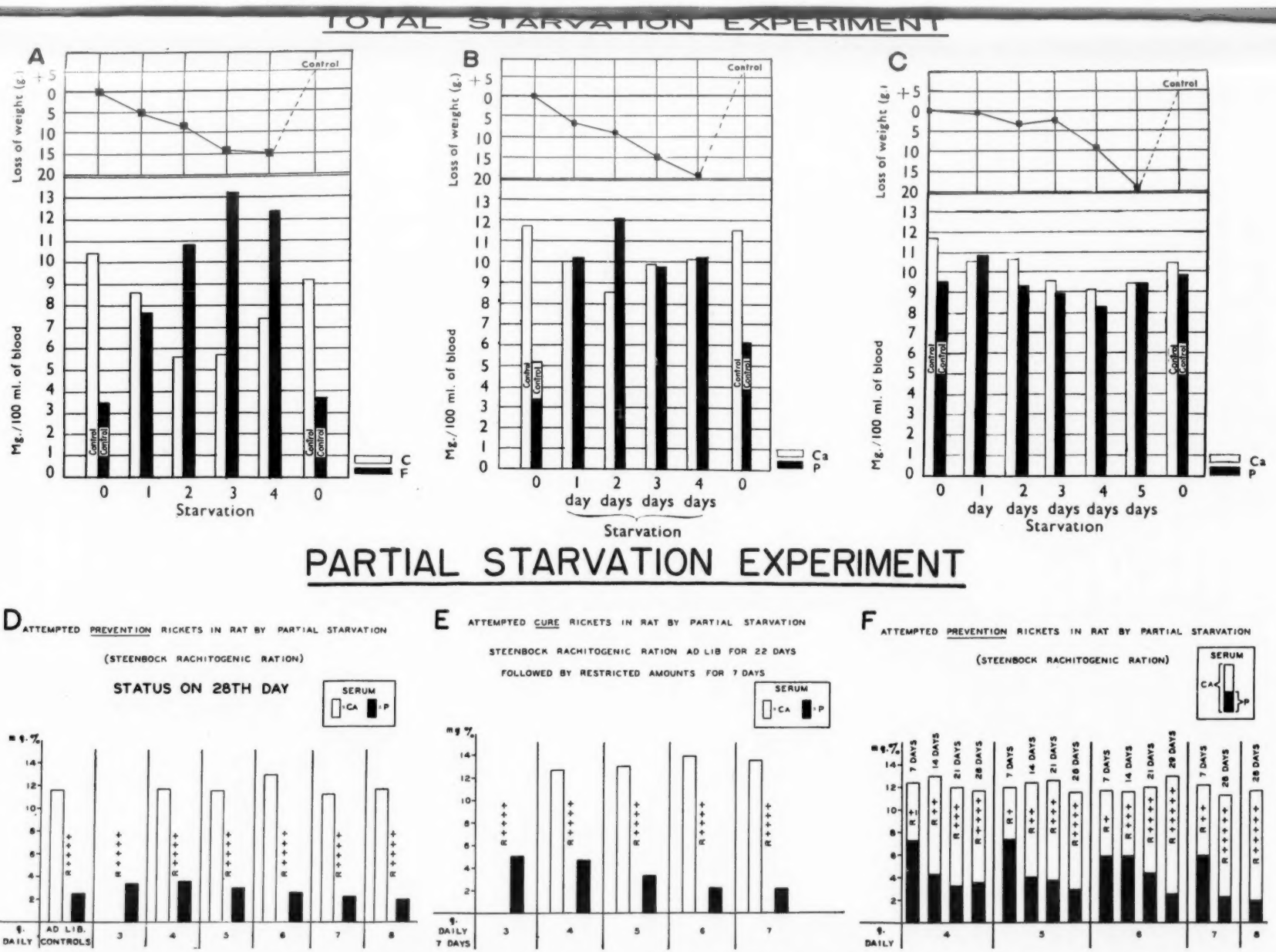

FIG. 6.—Diagram of experiments of the effect of total starvation on serum Ca and inorganic P. Pre-starvation diet: A, Steenbock rickets-producing diet; B, ditto, but rats protected by being irradiated daily with quartz mercury-vapour lamp; C, stock diet.

Diagram of experiments on the effect of partial starvation on serum Ca and inorganic P. Preventive: D. status on twenty-eighth day; E. ditto, weekly; Curative: F. status at end of seven days.

of the endochondral lesion in rickets to show how directly determined it is by the defect in the calcium-phosphorus equilibrium in the tissue fluids. I, therefore, now turn to the effects of severe illness on the calcifying mechanism in rickets, falling back first on experiments with the rat and afterwards on Follis's and my studies of rachitic children. As a preliminary, however, I must tell how extraneous illness could be conceived as affecting rickets.

How Illness could Promote or Oppose the Development of Rickets. Viewed from the 'pro' side, illness could precipitate or intensify rickets by diminishing the absorption of calcium and phosphorus from the gut and also the absorption of vitamin D. Associated acidosis could directly cause the loss of body calcium through its diversion into the kidney as a neutralizing base and at the same time could lower the renal threshold for phosphorus (Harrison and Harrison, 1952). It is easy to imagine that illness might interfere with the enzymatic reactions which end in the deposition of calcium salts in cartilage and bone and also with those specifically concerned with vitamin D action. I have demonstrated the visual effects of illness on the cells of cartilage and bone. The invisible chemical activities of the cells concerned with calcification may be interfered with all along the line.

From the 'anti' side I can think of only three ways in which illness could exert a healing influence, first through inanition, second through toxic effect, third by limitation of growth.

The experiments which I take up now all have to do with the action of inanition. Inanition is so often imposed by the severe infections that it may be considered almost a component part of their action. Moreover, in the nutritional group of Follis's and my series it appeared the central factor. Inanition could affect the body processes, so far as rickets is concerned, in two distinct ways; it could cause the liberation of phosphorus by forcing the body to feed on its own protein, and it could restrict growth. I was particularly impelled to study the effect of partial inanition on rickets, first because of the knowledge that total starvation did have a healing effect in rickets and, second, its investigation was simple. The information desired was, first, by what mechanism did inanition act and, second, could rickets be prevented and cured by partial inanition.

Experimental Studies in Rats

Effects of Complete Starvation on Rickets in the Rat. Years ago McCollum, Simmonds, Shipley and I (1922) demonstrated that starvation exerted a curative effect in the rachitic rat. The proof was the occurrence of a fresh calcium deposit in the cartilage topping the rachitic intermediate zone, exactly as in the vitamin D line test (Fig. 6A).

The Modus Operandi of Starvation. Dr. Elizabeth Harrison, working with me years ago at Yale University, made a study, never published, of the effects of complete starvation on the blood. This study showed why the deposition occurs. Rats just weaned, about 24 days old, were kept for 24 days on the Steenbock-Black ration and developed extreme rickets. At the end of the 24-day period a water diet was substituted. The inorganic phosphorus level of the serum rose from 3·5 mg. (control level) to 7·8 at the end of 24 hours, 10·9 at 48, to the maxima of 13·2 mg. at the end of 72 and 12·3 at the end of 96 hours. The calcium level dropped from 10·3 mg. % (control level) to 8·7 at 24 hours and lay at approximately 5·6 mg. % at 48 and 72 hours, rising to 7·4 at the end of 96 (Fig. 6A). Miss Harrison sought also—and this is not irrelevant, as will be evident later—to determine if radiation with ultra-violet light during the rachitic regime would prevent the marked shift in serum calcium and phosphorus. She found that it did make the rats resistant to starvation, since only a very slight shift occurred, nothing comparable to the degree in the untreated animals (Fig. 6B). She concluded that radiation with ultra-violet light either caused a better stocking of the skeleton with calcium or phosphorus—it prevented the rickets—or else preserved or actually increased the regulating power of the parathyroids. She also found that control rats fed stock diets showed, when starved, an almost complete stability of the calcium and phosphorus concentrations in the serum, a result favouring the first possibility (Fig. 6C).

Miss Harrison's experiments show the sharp rise in phosphorus and the fall in calcium which follow complete starvation. Evidently the rise in the phosphorus was enough to compensate for the lowering of the calcium. It produced an extremely abnormal equilibrium, resembling that seen in parathyroid tetany or more closely uraemia, which evidently, however, was capable of inducing precipitation. Miss Harrison's experiments also demonstrate beautifully the complete breakdown in rickets of the mechanism which regulates the calcium-phosphorus equilibrium in the body fluids. The radiated rats, synthesizing their own vitamin D, and those fed the stock diet were able to adapt so as to maintain during starvation normal calcium-phosphorus levels in the blood, whereas the rachitic rat was helpless. How does starvation work to

cause this sudden shift from the normal calcium and phosphorus pattern?

In complete starvation the glycogen of the tissues is rapidly used up, then the fat and protein are drawn upon. The protein yields phosphorus and it is the rise in phosphorus which is the factor responsible for the deposition of calcium salts. What actually happened in the rats of Miss Harrison's experiments is that the feed of the animal was abruptly changed from the rickets diet to its own tissues. This involved a transfer from a diet high in calcium and carbohydrate and extremely low in phosphorus and in fat to one high in fat and proteins, high in phosphorus and exceedingly low in calcium and lacking carbohydrate altogether. The rachitic rat, having lost all power to maintain the normal calcium-phosphorus in his body fluids became a prey to his diet and promptly reflected in his blood whatever the calcium-phosphorus pattern in the food happened to be. One could have obtained a shift in the calcium-phosphorus pattern identical with that induced by starvation by suddenly substituting for the Steenbock-Black rickets ration one high in protein and low in calcium and carbohydrate.

As a means of curing rickets total starvation obviously has only academic interest. By scaling downwards the amounts of food given, i.e. by partial starvation, we were hopeful of stopping rickets by stopping growth or by retarding it, and at the same time forcing the animal to metabolize his own tissues sufficiently so that the increased power of the blood to calcify would meet the requirement of the reduced new cartilage and bone formed. First I describe the partial starvation experiments planned to prevent rickets and afterwards the experiments planned to cure it by that means.

Attempts to Prevent Rickets by Partial Starvation. I now turn to unpublished experiments done years ago by Miss Deborah Jackson and myself to settle the point. Groups of rats, freshly weaned, were placed on varying quantities of the Steenbock-Black ration, namely on 3, 4, 5, 6, 7 and 8 g., respectively, per day. The plan was to kill them at the end of 28 days and then to measure the calcium and phosphorus in the pooled serum and examine the bones histologically. The group limited to the 2 g. amounts died within a few days and passed out of the experiment. Those on the 3 g. mostly died but six lived for the planned 28 days and all showed total rickets histologically. The groups on the 4, 5, 6, 7 and 8 g. amounts, when killed at the end of four weeks, also all showed severe rickets. The sole difference between the groups lay in the quantities of rachitic tissue produced. The rachitic intermediate zone (metaphysis) in the animals receiving the larger amounts of ration was much better developed, i.e. longer, than in those receiving the smaller amounts, indicating better growth, but absence of calcification was alike in all. The serum calcium levels in all groups were maintained approximately at the normal, 10 mg. % (Fig. 6D). The serum inorganic phosphorus levels, on the other hand, were much lowered in all and, it is important to note, again showed an inverse relationship to the food allowances; in the animals on the two smallest feeds, namely 3 and 4 g. per day, the inorganic phosphorus level was highest and it became proportionately less as the quantity of food increased. This result once more indicates that the body protein was catabolized inversely to the amounts of the feeds. As for the weights, the rats on the 3 g. allowance lost slightly, those on the 4 g., after initial loss, gained slightly and those on the larger intakes gained proportionately. The examination of the bones showed that all, including the 3 g. allowance group, grew in length, inversely, however, to the size of the intakes.

We thought it would be interesting to trace the evolution of the rickets week by week. Accordingly additional groups of animals on the 4, 5 and 6 g. daily allowances were killed seriatim after seven, 14, 21 and 28 days and one group on the 7 g. feed after seven days, the other after the full 28. The levels of serum calcium were normal in all, approximately 10 mg. % (Fig. 6E). The inorganic phosphorus levels, on the other hand, were highest, but just under the normal for the rat, in the seven-day groups and in the succeeding groups were progressively lower, reaching their lowest at the end of 28 days. The longer the period of underfeeding, the worse the rachitic state became, as judged by the phosphorus levels in the serum. When we began the semi-starvation experiments, we speculated that, if the underfeeding was continued long enough, the animals would be forced to burn increased amounts of tissue protein and the serum phosphorus level would progressively rise. But the contrary result is in accord with studies of starvation in human beings which show that the maximal destruction of body protein occurred initially and in a week or 10 days dropped to a lower level, as physiological adjustment developed (Benedict, 1915; Howard, Bigham, Eisenberg, Wagner and Bailey, 1946). Again, the values for the inorganic phosphorus tended to be higher, the lower the food allowance, referable to the greater sparing effects on body protein of the larger allowances.

So our attempts to prevent rickets by partial starvation with the Steenbock-Black diet failed entirely in both aims. Not even the smallest allowances prevented growth or caused even a partial healing.

Attempts to Cure Rickets by Partial Starvation. In a set of sibling experiments we tried to cure rickets by partial starvation. What we hoped to obtain by suddenly reducing the rickets diet, given before freely, to starvation levels was the healing stratum of calcification in the cartilage at the top of the rachitic intermediate zone (the positive 'line test') as in the total starvation experiments. We produced rickets in freshly weaned rats by giving the Steenbock diet freely for 22 days. Then in one group we abruptly reduced the ration to 2 g., in the others to 3, 4, 5, 6 and 7 g., respectively, and killed all at the end of seven days. All showed rickets without a trace of healing histologically. Again the calcium levels were normal (Fig. 6F), the phosphorus levels, at the end of the suddenly imposed week of partial starvation, showed an inverse relationship to the food allowance, once more indicating that the partial starvation had thrown the animals back on their own tissues, but even the smallest feeding was inadequate to produce any healing. These experimental attempts to elicit a curative reaction by partial starvation failed in contrast to the success with total starvation.

Significance of the Starvation Experiments. The Steenbock-Black diet is exceedingly high in carbohydrate, 70% of the calories. The protein, from vegetable sources, amounts to a little more than 20%. The calcium is in great excess, 1·2%, and the phosphorus very low, 0·28%. The ratio of calcium to phosphorus is a little more than 4:1. The diet is poor from the nutritional viewpoint; rats on it do not gain well. In that respect it seemed suited for prevention of rickets through prevention of growth. From the rickets viewpoint it is drastic, as shown by its preferential use for the line test, since with uniformity it renders the cartilage free of calcium. Herein lie the reasons why our partial starvation experiments turned out negatively. The excess calcium of the diet reduced the absorption of food phosphorus so that the quota of the latter in the serum coming in from the gut was kept low and the carbohydrate through its sparing action reduced the catabolism of body protein, so that the endogenous yield to the serum from that source was kept low. The combined action of these two factors prevented the phosphorus of the serum from rising to precipitation levels required by cartilage and bone.

Had we used a less drastic diet, one which caused only borderline rickets, and possessed at the same time better nutritive quality, permitting longer experimental periods, and had we also used older animals growing more slowly, I believe we could have succeeded in preventing rickets by underfeeding. We are about to attempt this.

Obviously the results of our experiments cannot be transferred to children. The rats all grew. It is doubtful if the child has anything like equal hardihood. Then, too, rickets is not natural to the rat. Given adequate calcium and phosphorus in the ration, it does not require vitamin D. Rickets has to be forced on it by gross defects in the dietary calcium and phosphorus. In contrast, rickets is natural to the child in the sense that he develops it, though the food is rich in calcium and phosphorus. In short the two are very different. But the experiments do have an important suggestive value. The effects of the food restrictions were all in the direction of prevention and cure. The greater restrictions forced the rats to use their body protein, as indicated by the rise in serum phosphorus, but the rise was insufficient to cause calcification. The results make it appear that the body tissues must be drawn on heavily; or, put the other way round, that a small sparing element in the diet may be enough to prevent the body from effecting its own cure.

We have not attempted the experimental study of the toxic factor. Such a study would be difficult of interpretation, though bearing more directly on the problem in the child, since its action might include starvation and be additive to its action by increasing further tissue protein breakdown and at the same time might work the other way round, supplying the factors which are provocative of rickets. We return now to Follis's and my studies on children.

Studies in Children

Proof that Illness can Precipitate Rickets. The provisional zone of the cartilage is the one closest to the shaft. Calcification there is always the most recent. If rickets had begun on Friday and death had occurred on Sunday, the defects in calcification of the cartilage would be limited to the provisional zone. Some time ago our attention was attracted to defective calcification of the provisional zone in our children showing otherwise exceptional heavily calcified lattices and for long we were puzzled (Fig. 7B). The overcalcified lattice of cartilage matrix extending up to the provisional zone proved that not a trace of rickets had been present in the earlier periods. Clearly, rickets had suddenly set in shortly before the end of life. Realizing that we had evidence that severe illness had precipitated rickets, we wondered whether it had operated by producing some local changes in the cartilage which

rendered it unable to calcify or had done so by creating some general disturbance in the calcium and phosphorus of the blood, as in ordinary rickets. Accordingly we appealed to Dr. Harold Harrison of the Harriet Lane Home to measure for us serum calcium and phosphorus levels during severe illness and again after recovery and found that he had already done this. Harrison's measurements showed plainly that in severe infections characteristic rachitic depressions of the calcium or phosphorus or both occur as indicated by their reduced values and rebound after recovery. Additional data, showing the same, were kindly furnished by Dr. Mitchell Rubin of Buffalo University Medical School. When we reviewed our cases of lattice formation in the light of Harrison's and Rubin's reports, we found evidence of terminal failure in calcification of the provisional zone in a considerable proportion. Illness can then precipitate rickets and does so in the ordinary way by affecting the calcium and phosphorus concentrations in the blood.

HARRISON'S MEASUREMENTS OF THE EFFECTS OF CA, P AND ALKALINE PHOSPHATASE IN SERUM*

Diagnosis	Acute Stage Serum			Convalescence Serum		
	Ca	P	Phospha-tase	Ca	P	Phospha-tase
Peritonitis ..	—	2·7	—	9·6	3·7	12·3
Empyema ..	7·3	1·8	5·4	9·4	6·9	14·2
Pneumonia ..	8·3	3·3	12·7	11·5	6·3	10·4
Meningitis ..	9·3	3·6	—	—	5·3	—
Meningitis ..	11·4	2·8	4·9	—	—	—
Infantile eczema	9·7	2·5	14·9	10·0	6·3	7·2
Cellulitis ..	8·5	2·8	5·9	—	—	—

* All measurements are in mg. per 100 ml.

It may now be anticipated that I go on to show that illness had caused moderate and severe rickets or had intensified its development. But this we were unable to do, for although the 'palaeontological' evidence might reveal that the rickets had suddenly begun or undergone an exacerbation, we could not date the event accurately enough to be sure it could not have preceded the illness. Indeed when it almost certainly fell within the illness, we could not prove that the development was not a natural one with which the illness had naught to do. We did obtain information from a study of trends, but of that later. I now turn to the opposite possibility: Did our studies show that illness could act like vitamin D on total starvation in the rat and cause a curative response in the form of the Müller stratum, commonly spoken of in x-ray parlance, as 'the line test'?

Can Illness Exert a Curative Effect? In 1858 Müller pointed out that in severe chronic rickets healing showed itself by the formation of a stratum or sheet of calcium salt deposit in the cartilage on the epiphyseal side of the rachitic intermediate zone, actually in what would have been the provisional zone of calcification if the rickets had never existed. The appearance of this line in the x-ray film is usually the first definite indication that healing is occurring. According to experience years ago, when severe rickets was common, 3 teaspoonfuls daily of cod liver oil (1,200 U.) produced the Müller shadow in the x-ray film quite regularly by the twenty-first day (Fig. 7C and D). In our series the earliest appearance was 13 days after the administration of 13,000 U. daily.

The reason that calcium salts fall selectively in this zone, in chronic rickets often far removed from the end of the shaft (Fig. 7E), is that it is the one where the cartilage cells contain the glycogen which appears to be implicated in the calcification process. Follis (1950) has demonstrated the presence of glycogen in this zone in rickets and its absence in the older cartilage below, i.e. that between it and the shaft. Apparently the rachitic cartilage loses its glycogen promptly if the calcium and phosphorus concentrations in the body fluids are insufficient to claim it, and the only reason we know why all the cartilage in the rachitic intermediate zone does not calcify at the same time as the provisional zone is that it has become *passé*, its glycogen being exhausted.

Did infections or severe states of malnutrition or the two in combination cause this line to develop in moderate or severe rickets?* Beginning with the second month and ending with the beginning of the twenty-third, there were 21 instances of a Müller stratum. In 15 of these its occurrence was explicable on the ground of vitamin D administration; either vitamin D had been given in the Harriet Lane wards or prescribed in the out-patient department or the mother asserted that it had been given. In an additional instance the stratum was accounted for by the administration of 3 g. of sodium phosphate daily over the last 17 days. Of the five remaining, in three, ages 11, 13 and 15 months, deaths had occurred in October, September and August, respectively, so that the presence of the stratum could have been accounted for by exposure to the summer sun. The nutrition in these three children was reported as 'fair' in one and 'good' in the other two. In the remaining two there was no explana-

* The sign is applicable only to cases of moderate or severe rickets in which growth has continued long enough so that the stratum of calcification will stand up on the cartilage to be clear of the shaft. It is not applicable in cases of rickets of very short duration in which it would be merged with the end of the bone and appear merely as an intensification of the calcification of the end.

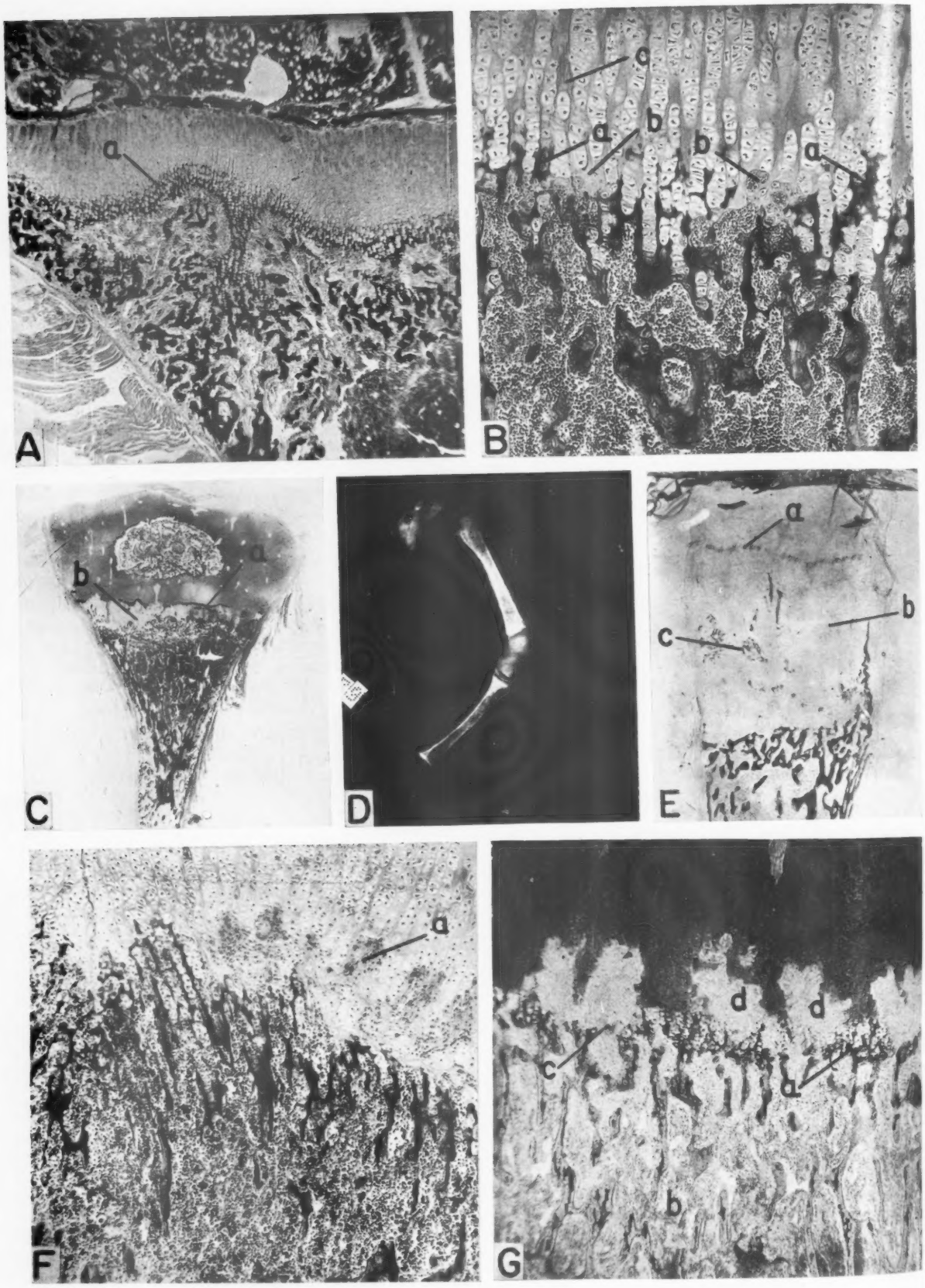

Fig. 7.

tion found other perhaps than the final illness (suipestifer septicaemia of 14 days' duration in one and protracted dysentery in the other). The nutrition was recorded in one as 'poor' and in the other 'actual emaciation'. Accordingly, in only two of the 21 instances can a healing effect be attributed to severe illness and in them the evidence is not certain.* The possible occurrence of a positive healing effect from illness and malnutrition in these two children is offset by our failure to find any evidence of similar healing in a considerable number of the subjects of severe rickets suffering from most severe protracted illness and severe malnutrition. Any antirachitic effect exerted by them must be small as compared to vitamin D.

* In the one death occurred in September, but it seems improbable that this 2½-months-old infant was exposed to the Baltimore sun. Moreover there was no information concerning vitamin D administration. In the other instance death was in February but four transfusions were given at scattered intervals and it is possible that haemolysis with liberation of phosphate may have occurred.

FIG. 7A.—(From H. Harrison) 266; × 15. Undecalcified Ag No_3, haematoxylin and eosin. (a) Fresh Müller stratum of Ca-salt deposit in 7-week-old rachitic cat produced by total starvation for 24 hours; serum Ca. 8·7, serum P 5·5 mg. %.

FIG. 7B.—502; × 60. Rib of 11-months-old child dying of generalized tuberculosis. (a) Lattice exhibiting (b) defective calcification of provisional zone, an observation first drawing our attention to the fact that illness can precipitate rickets; (c) pattern of matrix frame of cartilage which determines pattern of shaft, beautifully demonstrated.

FIG. 7C.—J.J.; × 3. Microscopic section, upper tibia from a child with severe rickets, treated with 1,200 U. vit. D (C.L.O.) for 21 days when death occurred. (a) Müller line of Ca-salt deposit; (b) rachitic metaphysis, appearing translucent in x-ray film (Fig. 7D) so that the Müller line there stands in relief.

FIG. 7D.—X-ray film of Fig. 7C after death.

FIG. 7E.—Rib from an unknown case of almost unbelievably severe rickets which evidently, from the appearance of the end of the shaft, must have begun suddenly and been total. (a) Müller stratum of Ca-salt deposit, far separated from end of shaft by (b), an enormously deep metaphysis in which lie (c) scattered deposits of Ca-salts.

FIG. 7F.—1363; × 40. Rib from malnourished 3-months-old child, dying of widespread tuberculosis. The histological preparation indicates the development of acute severe rickets, Ca-salt deposition having suddenly stopped completely. This is shown by (a) vascular-osteoblast complexes which have grown to huge, bush-like structures and protrude deep into rachitic cartilage. Undoubtedly the rickets began during the illness, but one cannot say that it might not have developed anyway. The illness showed no blocking effect, if it did not precipitate or intensify the development.

FIG. 7G.—897; × 17. Rib of 2-months-old child, dying of diarrhoea with dehydration of three weeks' duration; viosterol 6,660 U. daily for last 23 days. The histological preparation demonstrates the 'trend' of the rickets. Up to (a) the last stratum of Ca-salt deposit, the architecture of, (b) the shaft, looks normal; at (c) gaps in Ca-salt deposition denote beginning of rickets. From (a) on (upwards in the section) the rickets became total. The pale areas (d) represent huge vascular-osteoblast complexes, enveloped in osteoid, derived from the matrix substance of the cartilage; the dark areas separating them are composed of rachitic cartilage by-passed in the irregular invasion process (compare Fig. 5F). The 'trend' in this case was progressive development. Evidently, however, the rickets must have started before the relatively short terminal illness. No evidence of any vitamin D effect.

Does Illness Prevent Rickets by Stopping or Slowing Growth? As has been already pointed out, no growth, no rickets. Do our studies of children indicate that illness can prevent the disease in that way? Follis's analysis showed that of 147 children never having received vitamin D, 73 either had negligible rickets or none (Follis, Park and Jackson, 1952). Of these 73, 23 showed a marked inhibition of growth, if not complete cessation. In the other 50, growth had not stopped, as shown by histological examination. Our studies revealed, therefore, a group of growing children not requiring vitamin D. Obviously there is no way of knowing, if the 23, not growing, had resumed growth, whether they would or would not have developed rickets, i.e. if failure to grow was actually blocking the disease.

But thwarting rickets by ceasing to grow has only academic interest. If the child lives, growth will out. The question raises the larger one, then, of the relation of rickets to growth. Rickets must depend on a more or less fixed ratio of the rates of calcium and phosphorus supply available to the skeleton over the rate of skeletal growth. If the denominator, bone growth, is diminished, the requirement for calcium and phosphorus is diminished also. Theoretically, then, a small absorption of calcium and phosphorus, caused by a vitamin D deficiency, may be adequate, if the growth of the skeleton is correspondingly curtailed.

As a matter of fact proof that slow growth can prevent rickets is to be found in the individual subject of rickets. The rates of growth in the long bones vary as follows: Costochondral junction ++++++, lower femur +++++, upper femur, upper humerus and both ends of the tibia ++++, lower radius and ulna, the ulna being slightly the better, +++, the lower humerus ++ and the upper radius and ulna +, the ulna being the poorer. The histologist may find +++ rickets in the rib and none or only very slight evidence in the upper ulna. The rachitic state is general but the cartilage-shaft junction of the upper ulna fails to manifest it because the greatly restricted growth allows little new cartilage to form and that which does form lingers so long in contact with the tissue fluid that adsorption can exert its effect. In other words the rachitic state does not show there. The trabeculae underneath, however, will exhibit the same osteoid borders as those in the rib.

It does not follow from this that rickets is more prevalent in well nourished than in poorly nourished infants, for in the latter the factor of illness is more frequent, which may impair the calcium-phosphorus metabolism out of proportion to its interference

with growth. Rickets is more conspicuous in the well nourished child because the gross deformities are larger, but in our experience the severest examples of the disease actually have occurred in malnourished children. In the group never having received vitamin D, Follis's analysis failed to reveal a greater incidence of rickets in the well than in the poorly nourished (Follis *et al.*, 1952).

Trends. We tried to find if under the influence of illness the rickets was increasing or was being turned in the opposite direction toward healing. In the cases in which the natural movement of the disease could be traced in the bone, it was almost wholly in the direction of exacerbation (Fig. 7F).

Is Vitamin D Action Impaired? We hoped to be able to determine if the effectiveness of vitamin D was reduced in severe illness. However, the cases of our study offered too many variables and intangibles for analysis. We did find numerous examples in which during severe infections large amounts of vitamin D for more than five weeks failed to act. But here, as McCance (1947) has emphasized, different individuals vary so greatly in their requirement that conclusions were impossible. The cases of failure were, however, egregious and numerous enough to make impairment seem likely.

Summary

The earlier part of the lecture was devoted to the study of the growth pattern in uncomplicated rickets and its modification by illness. Under its influence the hyperactive cells lining the trabeculae withered and disappeared, and their growth activity ceased, an effect exactly like that seen in the non-rachitic bone. While the osteoblast could thrive in the low concentrations of calcium and phosphorus of the body fluids, the cartilage cell was incapacitated, being rendered unable to complete its normal maturation cycle necessary for the ingrowth of the shaft and its conversion into bone. In the light of this, the development of the endochondral lesion was traced and in general principle explained. The remainder of the lecture dealt with the effects of illness on rickets itself, i.e. on the abnormal calcium-phosphorus equilibrium in the tissue fluids which actually determines it. In order to explore this, the effects of the important factor in illness, inanition, complete and partial, were studied experimentally in the rachitic rat and the mechanism by which inanition exercises its antirachitic action was clarified. While complete inanition caused a deposition of calcium salts in the rachitic cartilage, partial starvation failed to produce any healing effect or to prevent the development of the disease or to stop growth wholly. In the child proof was offered that severe illness could precipitate rickets and that it did this by depressing the calcium and phosphorus concentrations in the blood, exactly as in vitamin D deficiency. The balance of evidence from several different sides favoured the view that the common influence of illness is to aggravate rickets already established. The relation of rickets to growth was considered and the conclusion reached that retardation of growth *per se* could exert a preventive influence. With the exception of two possible instances, the study of 21 rachitic children showing the Müller sign failed to disclose that illness, including malnutrition, could cause a healing action like vitamin D. It seemed probable that illness may affect rickets in two distinct ways, one favouring, the other opposing, and that generally speaking, the former is the more powerful and tends to predominate.

References

Benedict, F. G. (1915). *A Study of Prolonged Fasting.* Publication No. 203, Carnegie Institute of Washington.
Follis, R. H. (1950). *Metabolic Interrelations.* Trans. 2nd Conf., January 9, 1950, Josiah Macy Jr. Foundation, New York.
——, Park, E. A. and Jackson, D. (1952). *Bull. Johns Hopk. Hosp.*, **91**, 480.
Harrison, H. E. and Harrison, H. C. (1941). *Amer. J. Physiol.*, **134**, 781.
——, —— (1952). *J. Pediat.*, **41**, 756.
Howard, J. E., Bigham, R. S., Eisenberg, H., Wagner, D. and Bailey, E. (1946). *Bull. Johns Hopk. Hosp.*, **78**, 282.
McCance, R. A. (1947). *Quart. J. Med.*, **16**, 33.
McCollum, E. V., Simmonds, N., Shipley, P. G. and Park, E. A. (1922). *Johns Hopk. Hosp. Bull.*, **33**, 31.
Müller, H. (1858) *Z. wiss. Zool.*, **9**, 147.
Schmorl, G. (1909). *Ergebn. inn. Med. Kinderheilk.*, **4**, 402.

FATAL NEONATAL POLIOMYELITIS

BY

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(RECEIVED FOR PUBLICATION MAY 19, 1954)

During the present century one of the more noticeable changes in the character of poliomyelitis throughout the world has been a tendency for 'infantile paralysis' to become less common. This has been accompanied by a correspondingly greater incidence of infection in older children, and at the same time by an increase in the epidemicity and severity of the disease as a whole. Nevertheless, despite this general trend, during the years 1947-1951 inclusive, 1,147 cases of poliomyelitis in infants (aged 0-12 months) were notified in this country out of a total of 29,656 cases occurring in all age groups. A further analysis of the Registrar-General's figures for these years emphasizes the seriousness of the disease at this age, as 135 of the affected infants died (55 were under 6 months and 23 were under 3 months of age). In 1950, which was an epidemic year, there was a significantly higher incidence of paralytic disease in children under 3 months of age than in the remainder of the group (Logan, 1952).

Before 1948 published reports of poliomyelitis occurring in infants under the age of 6 months were few and were even rarer for the neonatal period (0-28 days). However, a recent review by Sims-Roberts and Thomson (1953) shows that an appreciable number of cases of poliomyelitis, many of them fatal, have been reported in young infants since 1947.

The case reported here is of an infant who died of poliomyelitis at the age of 18 days while in hospital under treatment for ectopia vesicae.

Case Report

G.W., a first born male infant, was delivered normally after a pregnancy complicated by maternal toxaemia, and was found to have ectopia vesicae and complete epispadias. He was transferred to The Hospital for Sick Children, Great Ormond Street, five hours after birth and on the second day of life surgical repair of the ectopia vesicae was undertaken. The bladder was inverted and the lower anterior abdominal wall was reconstituted over it. The immediate post-operative period was uncomplicated but the wound started to break down on the sixth post-operative day, and by the eleventh day after operation it had completely broken down so that the appearances of the lower abdomen now resembled those before the repair had been undertaken. These local changes were not accompanied by any constitutional reaction, and the only abnormal feature was a transient rise of temperature to 100° F. on the fourth day after operation (aged 6 days). When the baby was 16 days old breast feeding was begun but the child was sleepy and reluctant to take the breast. The following day flaccidity of the lower limbs was noted and later this extended rapidly to affect the arms as well; his colour was greyish and there was occasional twitching of the facial muscles. The blood urea was 23 mg. %. His condition gradually deteriorated throughout the day and he died the following morning (eighteenth day of life), approximately 36 hours after the onset of paralysis. The cause of death was not known, but the suggested clinical diagnoses included septicaemia, cerebral haemorrhage and adrenal haemorrhage; the possibility of poliomyelitis had been considered, but the age of the child was thought to vitiate this diagnosis.

Post-mortem Appearances

The necropsy was performed 22 hours after death. The body was that of a male infant, 21 in. in height and weighing 7 lb. The nutritional state was good and there was slight pitting oedema of the feet and legs. An oval skin deficiency was seen in the lower abdomen and there was an ectopic bladder with complete epispadias; the margins of the skin defect showed minor superficial sepsis.

The brain weighed 472 g. (average normal for the age 382 g.) and the parenchyma was oedematous, with poor differentiation between the grey and white matter and irregular punctate congestion in the region of both basal ganglia. Only the cervical portion of the spinal cord was examined and this revealed congestion of the grey matter. The right side of the heart was dilated and the myocardium of both ventricles was flabbier than usual, but otherwise appeared normal. The liver was fatty although its weight was within normal limits. Both lungs were oedematous and congested, but there was no evidence of consolidation. The remaining viscera

showed the changes of passive venous congestion.

Laboratory Investigations

In view of the history of paralysis a piece of the cervical cord was excised at necropsy and preserved at −20° C. Later an emulsion prepared from this tissue was inoculated intracerebrally into a rhesus monkey. On the third day after inoculation fine tremors of the ears, severe ataxia and paresis of the right arm were noted. The following day the temperature had risen to 105° F. By the seventh day paralysis of the legs and arms was evident and the animal was killed on the eighth day after inoculation. The brain and spinal cord were removed for histological examination.

Histology

Examination of the tissues from the child revealed the characteristic changes of acute poliomyelitis (Fig. 1). The individual lesions consisted of a variable meningeal reaction (lymphocytes, mononuclears and, occasionally, polymorphs in the subarachnoid space), partial or complete destruction of ganglion cells with neuronophagia, vascular congestion and perivascular cuffing with lymphocytes and polymorphs. There were also intraparenchymal collections of microglial cells and polymorphs as well as numerous small recent haemorrhages (Fig. 2). The lesions were in the grey matter of the spinal cord (affecting all horns, but maximal in the anterior); the medulla (affecting all nuclei, but minimal in the olives); the dorsal nuclei of the pons; the roof nuclei and superior vermis of the cerebellum; and the hypothalamus. There was some swelling of the ganglion cells in the pre-central gyrus.

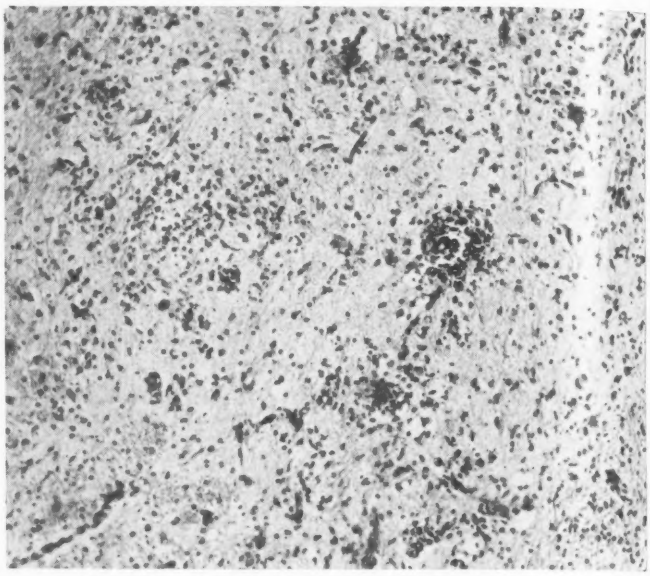

FIG. 2.—Cervical spinal cord, anterior horn: most of the ganglion cells have been destroyed, and the parenchyma is infiltrated with polymorphs and microglial cells. Haematoxylin and eosin × 90.

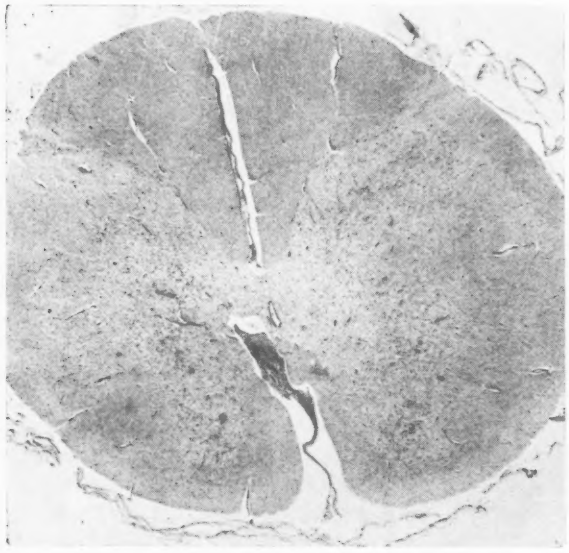

FIG. 1.—Cervical spinal cord: lesions are present in the grey matter of all the horns, but are maximal in the anterior horns. There is a well developed meningeal reaction. Haematoxylin and eosin × 16.

In the heart there were several microscopic foci of degeneration of the muscle fibres in the left ventricular wall, associated with a local infiltration with large, irregularly shaped mononuclear cells together with an occasional polymorph and lymphocyte. The muscle fibres were fragmented, and often appeared granular and more eosinophilic than usual; they had frequently lost their striations and many of the sarcolemmal nuclei were pyknotic. Occasionally the adjacent interstitial tissues were oedematous and contained large mononuclear cells.

Examination of the remaining viscera confirmed the macroscopic changes that had been noted.

The lesions in the brain and spinal cord of the monkey were essentially similar in nature and distribution to those seen in the child, except that fully developed changes were seen in the pre-central gyrus. In general, lymphocytes outnumbered polymorphs in the subarachnoid space and in the parenchyma.

Discussion

Although the naked-eye appearances of the brain and spinal cord of the infant were not so striking as to suggest immediately the diagnosis of poliomyelitis, the clinical history of sudden flaccidity of the limbs was considered sufficient to justify the preservation of a piece of the spinal cord with a view to subsequent inoculation. As the microscopical appearance in both baby and monkey corresponded to the histological pattern which has been considered diagnostic of poliomyelitis (Luhan, 1946; Howe, 1948; Bodian, 1949), there can be no doubt that the child suffered from this disease.

Some difficulty is encountered when an attempt is made to decide the means by which this baby became infected. But the three possible alternatives that present themselves are that the child was infected *in utero*, at birth (as, for example, by faecal contamination from the mother) or after birth. The fact that the mother was well during the pregnancy and puerperium, apart from a mild toxaemia, would make the first two modes of infection less likely, unless it is assumed that she suffered from a sub-clinical form of the disease. However, on the available evidence, and bearing in mind that the baby died at the age of 18 days and that the usually accepted incubation period is in the region of 10 days, it seems more likely that the infection in this case was post-natal. This belief is to some extent strengthened when it is recalled that the infant's temperature showed a transient elevation on the sixth day of life, 11 days before the paralysis was noted. It has not been possible to trace the source of the infection, although extensive enquiry was made. There were no other children in the hospital at the material time in whom a diagnosis of poliomyelitis was made; nor was there any history of the disease amongst visitors to the ward so far as is known, although clearly this only excludes those contacts with clinical disease. This apparently isolated incidence of a severe or even fatal form of the disease is not unknown in epidemiological experience and has been recorded recently in another case from this hospital (Pugh, 1952).

The Table summarizes the more important features of some of the recently reported cases of neonatal poliomyelitis and it is clear from this that only in some instances were the infants

TABLE 1

SUMMARY OF SOME CASES OF NEONATAL POLIOMYELITIS REPORTED SINCE 1947

Authors	Place and Date of Infection	No. of Cases	Age at Onset in Days	Place of Birth	History of Contact	Clinical Details of Infant	Pathological Details in Infant
1. Mouton *et al.* (1950)	U.S.A. 1948	5*	14, 18, 18, 21, 21	No comment	1 case: mother had paralytic polio. 1 case: sibling had paralytic polio	Paralysis of one limb or more. No deaths	Typical C.S.F. findings
2. Baskin *et al.* (1950)	U.S.A. 1949	2	4	Hospital	Mother had paralytic polio at delivery	Died aged 7 days	Typical lesions in C.N.S.
			8	Hospital	Mother developed paralytic polio 2 days after delivery	Died aged 14 days	Typical lesions in C.N.S. Acute focal myocarditis
3. Smallpeice and Ounsted (1952)	U.K. 1947	2†	21	3 cases all in same nursing home	No contact with known case of polio. Same nurse delivered all cases	Died aged 9½ weeks. Remained paralysed and mentally defective	No necropsy
4. Johns (1948)	U.K. 1947	1	4	Home	2 siblings had polio	Paralysed	
5. McConnell (1952)	U.K. 1950	1‡	16	Home	No comment	Died aged 25 days	Typical lesions in C.N.S. Acute focal myocarditis
6. Wright and Owen (1952)	U.K. 1950	1	8	Hospital	Mother developed paralytic polio day before delivery. Mother died	Died aged 10 days	Typical lesions in C.N.S. Acute focal myocarditis
7. Sims-Roberts and Thomson (1953)	U.K. 1952	4	13, 12, 10, 18	Same hospital	No obvious contact	3 died aged 16, 14, 11 days. 1 paralysed	Type III virus isolated from 2 cases and mother
8. Present case	U.K. 1953	1	16	Home	Admitted to hospital for operation on day of birth	Died aged 18 days	Typical lesions in C.N.S. Polio virus isolated from C.N.S. Focal myocarditis

* 5 additional cases reported under 6 months
† 1 " " " "
‡ 9 " " " "

possibly infected *in utero* (Johns, 1948; Baskin, Soule and Mills, 1950; Wright and Owen, 1952), although Sims-Roberts and Thomson (1953) regard this as unlikely: the problem is still not resolved. In the remaining cases, although the mode of infection is not obvious, the age at which the disease became manifest suggests that a post-natal infection was more likely. In these cases it is also highly significant that the affected babies were in the same hospital (Sims-Roberts and Thomson, 1953), or nursing home (Smallpeice and Ounsted, 1952), or came from families in which contact with poliomyelitis had been established.

The factors that determine the incidence of poliomyelitis in the first six months of life are undoubtedly complex but it seems probable that maternal antibody plays some part in protecting infants at this critical time. It might be expected that after exposure to infection the mother would develop antibody and, by transplacental transmission, protect her newborn infant provided that enough time had elapsed for the antibody to have reached a titre sufficient to afford protection. That this is not always the case is probably explained by the identification of several strains of poliomyelitis virus. Each strain has a specific antibody, so that a child born to a mother exposed to infection with one or other virus strain would have incomplete antibody protection and therefore would be theoretically at risk from birth.

The occurrence of visceral lesions in poliomyelitis is well known and, although it has been suspected for a long time that they resulted from dissemination of virus through the blood stream, the presence of a viraemia in the human subject has only recently been established (Horstmann, 1953). Myocarditis has attracted particular attention among both clinicians and pathologists, and the degree of involvement of the heart varies considerably from case to case. In the case described here the changes were not obvious macroscopically but consisted of microscopic focal lesions which could easily be overlooked unless they were sought for; in a case previously reported from this hospital the changes were gross and there was widespread destruction of heart muscle (Pugh, 1952). This previous paper summarized a number of the features from the reports in the literature, and it is interesting that most authors considered that older patients were more liable to develop myocarditis than younger ones. The incidence of myocarditis varied considerably in the reported series; six out of seven cases (Saphir and Wile, 1942), two out of 12 cases (Dublin and Larson, 1943), 10 out of 17 cases (Saphir, 1945) and 14 out of 35 cases (Ludden and Edwards, 1949). In the 17 cases reviewed in this paper myocarditis was present in four out of the eight fatal cases that came to necropsy (Table 1).

The diagnosis of paralysis in the neonate is often a difficult problem and in this child poliomyelitis was not seriously considered because of the early age at which symptoms developed. But epidemiological evidence and a study of the age of onset in the cases recorded in the literature show that paralytic poliomyelitis within the first six months of life is not as rare as has hitherto been thought, so that it should be included in the differential diagnosis.

Summary

A fatal case of acute poliomyelitis in a newborn infant under treatment for ectopia vesicae and epispadias is described. The infection was successfully transmitted to a rhesus monkey. The possible mode of infection and the occurrence of visceral lesions in poliomyelitis are discussed.

Our thanks are due to Mr. D. Innes Williams and Dr. Martin Bodian for permission to publish this case.

References

Baskin, J. L., Soule, E. H. and Mills, S. D. (1950). *Amer. J. Dis. Child.*, **80**, 10.
Bodian, D. (1949). "Poliomyelitis: Papers and Discussions presented at the First International Poliomyelitis Conference," p. 62. Philadelphia.
Dublin, W. B. and Larson, C. P. (1943). *Amer. J. clin. Path.*, **13**, 15.
Horstmann, D. M. (1953). *Lancet*, **2**, 90.
Howe, H. A. (1948). In *Viral and Rickettsial Infections of Man*, ed. Rivers, T. M., p. 245. Philadelphia.
Johns, A. W. (1948). *Med. Offr.*, **80**, 230.
Logan, W. P. D. (1952). *Monthly Bull. Minist. Hlth, Lond.*, **11**, 147.
Ludden, T. E. and Edwards, J. E. (1949). *Amer. J. Path.*, **25**, 357.
Luhan, J. A. (1946). *Arch. Path., Chicago*, **42**, 245.
McConnell, A. A. (1952). *Archives of Disease in Childhood*,, **27**, 121.
Mouton, C. M., Smillie, J. G. and Bower, A. G. (1950). *J. Pediat.*, **36**, 482.
Pugh, R. C. B. (1952). *Gt Ormond Str. J.*, **2** (no. 4), p. 118.
Saphir, O. (1945). *Amer. J. Path.*, **21**, 99.
—— and Wile, S. A. (1942). *Amer. J. med. Sci.*, **203**, 781.
Sims-Roberts, J. T. C. and Thomson, D. (1953). *Monthly Bull. Minist. Hlth, Lond.*, August, 152.
Smallpeice, V. and Ounsted, C. (1952). *J. Neurol., Neurosurg, Psychiat.*, **15**, 13.
Wright, G. A. and Owen, T. K. (1952). *Brit. med. J.*, **1**, 800.

THE EVOLUTION OF THE CONCEPTS OF INFANT FEEDING*

BY

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(RECEIVED FOR PUBLICATION MAY 3, 1954)

In those suspended moments of late night, midway between sleeping and waking, my thoughts drift dreamily to the subject and the matter of the Windermere Lecture. The thoughts come readily and they are masterly, indeed they border on genius, the phrases are limpid and poetic, their cadences have a majestic grandeur, a blending of sublime prose and poetry so subtle, smooth and lilting and so profound. Just what is appropriate for an honour so great. I must get up at once and write it all down while it is still fresh; such inspiration comes but rarely. Yet, I have it all quite clearly point by point, phrase by phrase, the apt similes, the poetic imageries, the noble prose, why not sleep and first thing in the morning . . . But alas, first thing in the morning it has all flown. Vague and formless thoughts without limpid phrase or prose or poetry or indeed substance are all that remain. I return from the facile fancies of my dreams—which would have made a superb lecture—to the mundane limitations of my waking hours and attempt to construct a lecture worthy of this occasion.

Paediatrics in the first two decades of this century in North America concentrated its greatest attention on infant feeding. A few other principles were emphasized such as the importance of examining the eardrums and the urine of the sick infant, a few eponymic diseases and symptoms were described but the gastro-intestinal tract in health and in disease received the greatest emphasis and there arose schools and methods of infant feeding. Like metaphysics, it was the search in an absolutely black room for an absolutely black hat that wasn't there! There were several black hats but not in the black room. They were before us all the time and it needed only the clearing of the mists before our eyes that they be seen.

In the first edition of *Holt's Diseases of Children* published in 1888 is a beautiful illustration. It is two pages wide and is unfolded in order to be seen. It represents the stomach capacities of infants at different ages. The illustration represents a number of post-mortem, rigor mortis stomachs, apparently filled with fluid, the volume held in these dead stomachs purporting to represent the capacities of live infant stomachs at various ages. From these momentous studies was evolved a rule of the quantity that may be fed an infant at any given age; it was 'age in months plus one'. Thus a 2-month-old infant may be fed no more than 3 oz. and so on. Some inconsiderate infants did not know this rule and their vocal demands for more food was called colic, and this in turn gave rise to more and diversified ideas on the causes of colic, its prevention and treatment, but never to the idea that the hungry baby might appreciate being made an exception to the hard and fast rule of age in months plus one. The breast-fed infant went merrily on feeding, sleeping and gaining, until one day some inspired pediatrician invented test weighing. This brought to light a number of infants who had no regard for the rule whatsoever; some who at 5 or 6 weeks of age were found to consume as much as 5 or 6 oz. at a time and this after only a few minutes at the breast, despite the dictum of the sages that the infant must nurse at the breast for 20 minutes, shorter periods, of course, leading to gastric distension and to colic. However, a new fact must give birth to a new theory. There developed the concept of the anatomic capacity of the stomach—age in months plus one—and the physiological capacity of the stomach, amount undetermined. Armed with this new theory one could now proceed to the obvious, namely to permit the infant to determine his quantity of food by the simple device of permitting him to follow his own desires.

The disastrous results of artificial infant feeding —or hand feeding as it is called in England—was of course one reason for the emphasis then laid on breast feeding and on wet nursing. There was the

* The Windermere Lecture given before the British Paediatric Association at Windermere on April 29, 1954.

noble and almost missionary work of Sedgwick which came almost to naught with the later improvement of ideas and methods of artificial infant feeding; but in this era of confusion Sedgwick's work was life saving. The era was not without its humour, not the least of which was Osler's impish joke at a dinner in New York in the year 1900 celebrating the seventieth birthday of Abraham Jacobi. Osler was a member of the American Pediatric Society and its third president. In his speech at this dinner in the midst of his complimentary remarks about Jacobi, as Cushing remarks, his alter ego, E. Y. Davis, got the better of him and in all seriousness he spoke as follows:

> 'There is no single question before the nation today of greater importance than how to return to natural methods in the nurture of infants. The neglect is an old story in Anglo-Saxondom. St. Augustine, so Bede tells us, wrote to Pope Gregory complaining that the question of infant feeding was worrying him not a little! I understand that a systematic effort is to be made to supply every child born in this land its rightful sustenance for one year at least. Under the auspices of the Pediatric Society and the Women's Christian Temperance Union, a Women's Infant's Suckling Union is to be established, which will strive to make it a criminal offence against the State to bottle feed any baby, and which will provide in large and well equipped sucklingries ample sustenance when a mother from any cause is unable to do her duty. Dr. Rotch tells me that the action on the part of the Pediatric Society has been influenced by an exhaustive collective investigation which has been made on the future of bottle-fed babies, in which it is clearly shown that intellectual obliquity, moral perverseness and special crankiness of all kinds result directly from the early warp given by the gross and unworthy deception to which it is subjected—a deception which extends through many months of the most plastic period of its life. According to these researches you can tell a bottle-fed man at a glance, or rather at a touch. Feel the tip of his nose. In all sucklings the physical effects of breast pressure on the nose are not alone evidenced in the manner set forth so graphically by Mr. Shandy, but in addition the two cartilages are kept separate and do not join; whereas in bottle-fed babies in whom there is no pressure on the tip of the nose the cartilages rapidly unite, and in the adult present to the finger a single sharp outline entirely different from the split bifid condition in the breast-fed child. The collective investigations demonstrate that all silver democrats, many populists, and the cranks of all descriptions have been bottle-fed, and show the characteristic nose-tip. Utopian as this scheme may appear, and directly suggested, of course, by Plato, who can question the enormous benefit which would follow the substitution of sucklingries for Walker-Gordon laboratories and other devices! . . .'

The appalling mortality of infants during the first year of life together with the vague, controversial and often ineffective methods of infant feeding, lent, of course, an increased importance to human milk as a way out of the difficulties. This led to the development of methods of collecting and storing human milk, which at best was in such short supply that it was used very sparingly almost like a medicine. An ounce might be added to the whole day's cow's milk mixture, and this only in the desperate cases.

In Boston and in New York during my days as house officer there were district nurses whose business it was to follow up those mothers who left the lying-in hospitals still nursing their babies and to offer to buy their excess of milk. The mothers were instructed in the method of stripping their breasts and were paid about six cents an ounce for the product. The 'milkmaids' would leave the hospital in the morning with empty sterilized feeding bottles and would return towards evening laden with the day's milking. In order to enhance their earnings, the mothers were not above adulterating their milk. They either added water or they added cow's milk. It was my duty to attempt to detect the frauds by testing the specific gravity and by making a fat analysis. With these and other tests we could usually detect the impostors and buy no more of their inferior product.

Wet nurses were a quarrelsome and in other ways a troublesome lot. They were housed in the hospital and their infants boarded in the same institution. Most of these were homeless women of low intelligence and morals. The milk obtained under supervision was naturally of good quality but the quantity produced hardly warranted the trouble and expense of keeping them. They were all imbued with feelings of indispensability which made them insufferable. The practice was short lived.

The textbooks of the day, in dealing with wet nurses emphasized the importance of the character of the wet nurse—she must be good natured and calm. I have often wondered if this was not a relic of the days when it was believed that the infant sucked character from his nurse. 'Thy valiantness was mine, thou sucks't it from me' or 'From my dugs he drew not such conceits'—I think these phrases, in the beliefs of the times, had more than a symbolic meaning.

Cardinal Riccardo Petroni, of Siena, who died in 1313, was disgusted with the vulgar Italian tongue and the quality of ecclesiastical Latin of his day and left elaborate provisions in his will for the importing of Latin-speaking wet-nurses and for the founding of the Petronian College of Latin-speaking Wet-nurses. The idea was not carried out until 1719. Their infants were to hear nothing but Latin and only before going out into the world were they to

be taught sufficient Italian to avoid their being taken for illiterate ignoramuses. Needless to say, the project did not long survive—but wet nursing survived until the dawn of the present era of better understanding of the nutritional needs of the infant and of how by simple means to provide them.

There was then, as now, never enough breast milk to go around and the problem of artificial feeding as it was called, was ever present. To quote L. Emmett Holt Junior, from his preface to a little book on *Modern Trends in Infant Nutrition and Feeding* by Jonathan Lanman:

> 'To the student of infant feeding whose training goes back to the early part of the present century, the subsequent decades of American pediatric history have brought the painful necessity of unlearning many of the gospel truths instilled by his preceptor. Infant feeding was then not only a science; it was a fine art. The vitamins were still unborn, and amino-acids formed no part of the clinician's vocabulary, but the task of juggling the percentages of protein, fat and carbohydrate to suit the child's digestion was sufficiently engrossing and complex. We knew the percentages of these food-stuffs that could be tolerated and what would happen if this tolerance were exceeded. We worried about curds, about the harmful effects of volatile fatty acids and the potential laxative effects of various carbohydrates. We knew the cause of digestive disorders; they were, of course, due to the food—too much of this or that had been given. We knew in general what to do for these disorders, but it was reserved for the skilled pediatrician to manage the "difficult feeding case"—to use the food materials of that day and with a master's touch to avoid the Scylla of indigestion and the Charybdis of inanition. When he failed there was always breast milk to turn to as a last resort; the wet nurse was still in her hey-day, and the breast milk dairy prospered.'

The search for a satisfactory substitute for human milk is probably as old as history. Itself a fruitful subject for research and amusement but far too long a story for this short hour. Paps, milk from various animals, direct nursing from the animal—as with Romulus and Remus—dilution, addition of honey, all these have had some vogue. By the time Oliver Wendell Holmes wrote the story of Iris in his *Professor at the Breakfast Table* it was already the custom to dilute cow's milk and add sugar.

Iris was the child of a poor school teacher. The mother died at Iris' birth. This is how Holmes puts it:

> 'The poor lady, seated with her companion at the chess board of matrimony, had first pushed forward her one little white pawn upon an empty square, when the black knight, that cares nothing for castles or kings or queens, swooped down upon her and swept her from the larger board of life.'

So poor Iris was left without a mother to feed her. The boys of the school presented the poor tutor with a silver goblet. It was apparently a feeding boat for, as Holmes puts it, 'The handle on its side showed what use the boys had meant it for, and a kind letter in it, written with the best of feeling, in the worst of Latin, pointed directly to its destination.' Then he goes on, 'Out of this silver vessel, after a long, desperate strangling cry, which marked her great first lesson in the realities of life' (remember Lear—'when we are born we cry that we are come to this great stage of fools'), 'the child took the blue milk, such as poor tutors and their children get, tempered with water, and sweetened a little, so as to bring it nearer the standard established by the touching indulgence and partiality of nature—who has mingled an extra allowance of sugar in the blameless food of the child at its mother's breast, as compared with that of its infant brothers and sisters of the bovine race.'

It was probably Bidert in 1905 who started some of the trends in infant feeding at the turn of the century. His studies in the chemical composition of human milk and the inevitable comparisons with that of cow's milk led to the simple conclusion that all that was required was to so alter cow's milk by dilution, addition of cream, addition of lactose, so as to make it as nearly as possible similar to human milk. Thus arose the cult of similarity. Followed to its logical conclusion it led to ridiculous attempts to simulate human milk—ridiculous, though often ingenious. Top milk mixtures, whey and cream mixtures, attempts to so regulate the content of lactalbumin and casein and salts so as to be 'exactly' like human milk. The observation that the fat droplet in cow's milk was much larger than in human milk led to the use of homogenized milk in which the fat droplets were smaller. This did not prevent the professor from administering a teaspoonful of olive oil at a time—unhomogenized—if it was indicated—of all things—for constipation! or of three teaspoonfuls of pure cod liver oil, not even emulsified when the word vitamine, spelled with an 'e', came into the language—these were medicines and did not count. It is interesting in connexion with cod liver oil to review the opinions of the giants who trod the earth in those days with reference to the efficacy of this medicine. Cod liver oil was a folk remedy for rheumatism in the eighteenth century. From rheumatism it extended to gout and from gout eventually to rickets. Still taught that the increased amount of fat increased the absorption of calcium and felt that any oil would do as well. His mixture of vegetable oils, however, contained pilchard oil and this mixture, he held, though not as palatable, was equally effective. Pilchard oil, of course, is a rich source of the

antirachitic vitamin; but Still did not know this. The Germans, Czerny and Finkelstein, while they did use cod liver oil did not trust it without a little phosphorus, while Holt held to the idea that the fat itself was important, and during the First World War dispensed cotton seed oil to which was added one drop of oleum phosphoratum to every six ounces. He assured us that this was just as good!

Coming back to the cult of similarity, it was Gerstenberger who laboured long and diligently to produce a milk, or rather a food, that was in all possible respects similar to human milk. Similar in the content of volatile fatty acids, in the iodine number of the fat, in its congealing and melting points; similar, too, in the quantity and distribution of its mineral salts. He called this mixture 'synthetic milk adapted' and most of it had never seen a cow! S.M.A., as it is known in America, is still widely and I may say, successfully used even though the necessity of going through such chemical acrobatics has long since passed. Gerstenberger's mixture of fats contained tallow oil, cocoanut oil, cocoa butter, cod liver oil and tallow, this in order to show that replacing the butter fat mixture with a fat with the low volume fatty acid content of breast milk 'would change the dyspeptic character of the stools'.

This preoccupation with excreta by paediatricians from the turn of the century to the early twenties forms one of the most amusing chapters in the history of infant feeding. It was the coprophilic era, or the era of divination by stool. Just as in the Middle Ages diagnoses were made by inspection of the urine ('carry his water to the wise woman'), so in this era was far more attention paid to the stool than to the infant. Many a surviving American paediatrician of that era remembers the fetish that was made of the stools in those days. A young and progressive paediatrician travelling abroad would often bring home with him a complete set of moulages depicting in realistic—dare I say lifelike—form every variety of stool in every conceivable, real or imaginary, digestive derangement. Students were taught from these moulages and they were examined on them. The professor himself was, as you may imagine, the expert. A familiar scene in the days of the old Boston Floating Hospital is typical of the practices of the day. It was the ward nurse's duty to keep on hand a specimen of each child's stool. In time for ward rounds, she had these specimens neatly done up in brown paper, with the infant's name in the upper right hand corner. These were placed in a basin in alphabetical order and it was the duty of the junior interne to hold this basin in his arms, at a safe distance from the professor and his assistants and visitors, and to come forward with the specimen whenever the bed of a given infant was approached. The professor carried a handful of wooden spatulas in his breast pocket, but I do not remember him ever using it for examining an infant's throat, it was used to smear the specimen of stool, to note its consistency, to search for curds—soap and bean—with never a look at the infant, but only from this meticulous examination on which he would expatiate lengthily and eruditely, he would finally offer the suggestion for the next day's food. The order would be either increase or decrease the fat, the sugar or the protein by, usually, one quarter of 1%. No regard, mark you, for the variations in the content of these substances from day to day in commercial milk, but a change from a mean figure chosen from someone's text. All this from the mere inspection of a stool sample. In his later years, L. Emmett Holt Sr., began to see the futility and the senselessness of this coprology. I remember when I was his house officer he was examining a severely marantic infant whose progress had been consistently downhill despite his best efforts. A junior interne came forward to show him what a good stool the infant had just passed. Holt's comment was, 'Well, at least he'll die with good stools'. It is much like the modern cynicism about the patient in an oxygen tent, 'At least he'll die with a good colour.'

The sugars gave the paediatricians of those days a worrisome time. The cult of similarity taught that the only sugar suitable for infant feeding was lactose, and this despite its expense was the sugar commonly used. Sugar of some kind must have been used as an addition to milk from time immemorial. In Isaiah VII verses 14 and 15 we read: 'A young wife shall become pregnant and give birth to a son named Immanuel. He shall be fed on rich milk and honey.' Yet in the intestinal derangements of infants sugar was the villain—even lactose. Fermentative diarrhoeas were rife, and all of these, diagnosed by inspection of the stools, were 'obviously' caused by the fermentation of the sugar. Therefore non-fermentable sugars were recommended and preparations containing various proportions of dextrins and maltose came into use. Polycarbohydrate feedings became a short vogue—a little lactose, malt sugar, sucrose and some starch, to dilute, as one author of the time put it, the injurious effect of each. Oscar Schloss dared to increase the carbohydrate content of feeding mixtures up to 20% in order to show that the sugar was not a factor in the causation of so-called fermentative diarrhoeas.

It was John Howland who put the quietus on any sugar controversy. During the first World War the price of lactose rose to $1.25 per pound and thus became prohibitive for people of modest means. He dared to use sucrose as the only carbohydrate and it rapidly became evident that no other sugar was required.

The cult of the acids forms an interesting chapter in the development of rational ideas of infant feeding. Despite all our theories with reference to the dilution of cow's milk, it has been known for centuries that milk fermented with lactic acid bacilli could be well tolerated undiluted. In the scientific era this was taught to be due not to the acidity of the milk but to the effect of the bacilli, Metchnikoff was the great exponent of this theory. Did he not teach that by drinking fermented milk one could live to be a hundred. Metchnikoff while drinking this milk died at 71. Yet the idea persisted that there was some benefit from the bacilli themselves until Marriott wondered if it were not the acid rather than the bacilli that made soured milk more easily tolerated. He showed very simply that the buffers in cow's milk were such that it required three times as much decinormal hydrochloric acid to bring it down to a *p*H of 6 than it did when breast milk was used for the experiment. He reasoned therefore that the gastric hydrochloric acid of the infant was used up by the cow's milk and was therefore unavailable for peptic digestion. This is probably still true for the sick infant and one might at times be well advised in some cases still to use acidified milk, but it hardly applies for the well infant. There followed at this time a veritable epidemic of papers on acidifying milk. Each new acid produced a new paper: Alfred Hess with lemon juice, several others with citric acid, vinegar, nitro-hydrochloric and hydrochloric acid. This last deserves some mention.

One of the contributors to the question of acidified milk was Harold K. Faber. He found that by the addition of 25% decinormal hydrochloric acid to sweet milk, the *p*H could be lowered to 6 without appreciably altering the taste. This was published in 1923. It was about at this time that the important work of Gamble, Ross and Tisdall appeared on the effect of acid-producing substances in the control of infantile tetany. They showed, in effect, that it was not the calcium in calcium chloride that controlled infantile tetany but rather that it was the chlorine ion; that ammonium chloride would do as well. Long before this, Emmett Holt had taught that calcium lactate had no effect on tetany, but that calcium chloride had. This was the empirical observation of a great clinician. What Faber did with his hydrochloric acid milk, for me at any rate, was to teach me a very simple and most effective way of treating tetany. Hydrochloric acid milk never became a vogue and now is probably never used; yet in the spring of the year, when the paediatrician's fancy lightly turns to thoughts of tetany, my thoughts turn to hydrochloric acid milk. It requires only the addition of 25 ml. of decinormal hydrochloric to each 100 ml. of cold milk, sweetened in the usual way, to control the infantile tetany which we still see in Canada in the spring of each year. Thus Faber's paper was not written in vain.

The combined ideas of the harmfulness of sugar and of the benefits of acid milk had led Finkelstein some years before to invent *Eiweiss milch*, later called albumin milk, and finally protein milk. Through many complicated contortions a milk was produced that was high in fat, high in calcium caseinate, low in lactalbumin and low in sugar. The idea was first that by reducing the quantity of sugar, the fermentation in the intestine was reduced and by increasing the relative proportions of fat and calcium caseinate, the insoluble soaps in the stool were greatly increased, thus leading to a stool of firmer consistency. This is quite true—for the well baby or for the baby with a short-lived or self-limited diarrhoea—but for the sick infant with rapid peristalsis it is a different story. The vogue of protein milk has far from died out and the exact teachings of our paediatric forebears have been replaced by a vagueness as to its origin and its purpose. Our newer concepts of the relation of parenteral infections to diarrhoeas, the use of antibiotics, the search for and elimination of sources and, above all, the use of intravenous solutions for the maintenance of fluid and mineral balance should long ago have relegated protein milk to the limbo of forgotten things. Protein milk, when it was effective, was a cork; it paid more attention to the character of the intestinal contents than to the biochemical and the fluid equilibrium of the infant.

For reasons which are difficult for us now to understand heated controversies raged on both sides of the Atlantic over the question of boiling milk for infant feeding. Apparently boiling of milk was harmful. Vitamins were destroyed, enzymes were destroyed. The fact that bacteria were destroyed and that vitamins (only vitamin C was affected) could be provided in greater abundance from other sources did not seem to bear much weight with the zealots. The enzymes were said to be very important, but just how or why and whether replaceable or not were questions to which straightforward answers were not to be had. The Walker Gordon Milk Laboratories were established in 1891.

Their purposes were first to produce certified milk. This was a raw, unpasteurized milk produced with the greatest possible cleanliness from tuberculin-tested herds. Bacterial counts as low as 2,000 per cubic centimetre were not uncommon. The other purpose was to establish laboratories for preparing the baby's formula. Certified milk sold at that time at 25 cents the quart when milk of lesser quality sold at from six to nine cents the quart. The day labourer earned a dollar a day and the office clerk from 12 to 20 dollars a week. It was obvious that certified milk was not for the masses and that no problems were solved by this luxury. The apogee of this luxury was the formula department. At a cost of about one dollar a day the milk laboratory would prepare the infant's formula according to the doctor's prescription, divide it into sterilized feeding bottles and deliver it daily in a miniature refrigerator to the fortunate household. The poor darling of the rich, the mother, was thus spared the trials of preparing her infant's intricate formula, of giving an hour of her precious time to such menial tasks and was saved from the danger of adding an ounce too much milk or an unlevel tablespoonful of sugar. The prescription was a doctor's prescription, complete with the reputed sign of Jupiter. It was, of course, far too simple to order so many ounces of milk, so many of water and so much sugar or lactose. One wrote on this prescription something like this: Fat 2·75%, carbohydrate (lactose) 6·5%, protein 1·8%, six feedings, 5 oz. each—let the technician figure it out, no doubt with a slide rule.

The problem of vomiting or the passing of tough casein curds had to be solved. Raw whole milk entering the infant's stomach is converted into a solid mass of casein; the late Joseph Brenneman called milk 'one of the most peculiarly and uniquely solid foods that is ever used'. These huge curds which could be vomited and which could cause death by aspiration could also pass through the intestine scarcely touched by proteolytic enzymes or bacteria. Since milk must not be boiled, some means must be found to reduce curd tension. The cereal diluent was ideal for this purpose. Hence barley water and oatmeal gruel; the colloidal action of these substances permitted the formation of soft, flocculent curds. Soured milk, acidified milk, boiled milk, gelatin were all effective and had their advocates, but at last the scientists demonstrated that passing ultrasonic waves through milk produced a flocculent curd and thus the problem was for ever solved. But this solution came at a time when there was no further need for it, for the boiling of milk for infant feeding had by now become almost universal.

Since certified milk solved no problem on any large scale, it was left to Howland to use what was called grade 'B' milk boiled for sterilization, with about 5% of cane sugar added. Vitamin C had long since been added to the diet of all artificially fed infants and now it only remained for Howland, Hess, Chick and many others to clarify the real purpose and the need of cod liver oil as a regular supplement to the infant's diet. The conquest of rickets was well on the way, infants began to thrive and paediatricians became physicians for the young of the race instead of highly paid nannies.

The prejudice against evaporated and dried milks, very strong at one time, was quickly overcome by Marriott and through him the use of corn syrup became very popular. We physicians are ever addicted to playing the great game of follow the leader.

Out of this simplification of infant feeding there evolved three simple principles, whatever the method. They are adequacy, sterility and accessory factors. The provision of an amount of whole milk sufficient to meet the fat and protein requirements of the infant, and the addition of sufficient sugar, any sugar, to supplement the caloric deficiency of the milk allowance with sufficient water to meet the fluid needs of the infant and the provision of adequate vitamin supplements. It is interesting to observe that in other days milk was diluted because it was 'too strong' for the baby; now, however, water is added only in order to supply a need for fluids. We are still doing the same thing, but the reason is different. The boiling of the milk mixture not only insures its sterility but solves the curd problem as well while the addition of vitamins C and D have made rickets and scurvy a mere memory.

So has what loomed as an esoteric subject a mere 30 years ago has turned out to be what it always should have been—simple and obvious.

The late John Rurah sketched the whole history of infant feeding humorously in a short poem which ends as follows:

> A hundred years will soon go by
> Our places will be filled
> By others who will theorize
> And talk as long and look as wise
> Until they too are stilled.
> And I predict no one will know
> What makes the baby gain and grow.

ESSENTIAL PULMONARY HAEMOSIDEROSIS AS AN IMMUNO-HAEMATOLOGICAL PROBLEM

BY

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(RECEIVED FOR PUBLICATION APRIL 5, 1954)

The 30 cases of essential pulmonary haemosiderosis hitherto published supply ample data to present not only the classical pattern of this disease but also its latent form. The condition mostly affects children; in adolescents (16 to 20 years of age) it was observed in two instances only (Waldenström, 1944; Walton and Williams, 1951) and the true nature of the adult cases reported by Borsos-Nachtnebel (1942) and by Ellman and Gee (1951) is still disputed. The collapse-like state repeatedly occurring at intervals of weeks or months is characteristic of the disease, whose predominant symptoms are cachexia, fatigue, pallor and cyanosis, dyspnoea and cardiac insufficiency; haemoptysis is frequent and at other times haematemesis, with abdominal complaints. The fingers may become clubbed.

The skin is pale, sometimes more or less icteric, and in certain cases bluish pink. The radiological findings may—in rare instances—be entirely negative or show large foci or an intense density in both lungs, but in a considerable number of cases the change suggests miliary tuberculosis. After the attacks the intensity of radiological signs may decrease, remain unchanged or occasionally progress. In the presence of characteristic symptoms diagnosis is not difficult. The fewer the symptoms the more difficult it is to differentiate the condition from iron-deficiency or haemolytic anaemia, or the radiograph from that of miliary tuberculosis. In the latent form bronchitis alone may be the guiding symptom (Scheidegger and Dreyfus, 1945). In the initial stage recognition of such a case may be possible only by special means. As long as the disease could not be cured and was attended by a 100% mortality, early diagnosis had no particular significance. Since, however, independently of each other, in England Paterson (1946), in Portugal de Castro Freire and Cordeiro (1948; Cordeiro, 1952) and in Hungary Steiner in 1952 have attempted not only to check the progress of the disease, but also to make it regress by means of splenectomy, diagnosis in the early stage is of paramount importance.

Report of a Case

U.G., a boy, of 6 years of age, had been treated since October 11, 1950, in different hospitals because of weakness and anorexia; on one occasion the sputum had contained blood. A systolic murmur, marked anaemia (Hb 20%, R.B.C. 2,000,000), anisocytosis, poikilocytosis and increased haemopoiesis in the bone marrow had been found. Radiology had revealed a somewhat dense hilar structure and an enlarged heart. On treatment with iron, vitamin B and liver extract, the haemoglobin had increased to 60% and the red cell count to 3,500,000 per c.mm. The child was admitted to our department on five occasions, always on account of sudden malaise and extreme weakness. At the first admission, in July, 1951, he was an underdeveloped, undernourished boy with a yellowish skin, and somewhat enlarged submental and inguinal lymph nodes. The lungs were normal. The heart was slightly enlarged to the left, with a systolic murmur. The pulse was weak at 130 per minute. Radiographs gave a negative picture of the lungs, but the heart was slightly enlarged to both right and left and almost spherical. An electrocardiograph showed the electric axis deviated to the left, a sinus rhythm, tachycardia and a slightly depressed St_1.

Laboratory Findings. The red cell count varied during attacks between 1,600,000 and 2,800,000 per c.mm. After treatment it rose to 3 to 4,000,000. Haemoglobin was 20 to 30% on admission and 50 to 80% before discharge. The white cell count rose from 3,400 to 28,000 and differential counts were normal or shifted to the left, frequently with 10 to 26% eosinophils. Anisocytosis, polychromasia, pseudo-macrocytosis and microcytosis were marked. The reticulocyte count varied from 70 to 230 per thousand cells and became normal when the general health improved. Erythrocyte resistance was often normal; in many instances it was found to be decreased.

Bone marrow counts are presented in Table 1. Myelopoiesis and erythropoiesis were normal but greatly accelerated. While the normal proportion of myeloid to

erythroid elements is 3 to 1, in our case it was 0·6 to 1 or 1 to 1. The colour index was as a rule below 1, sometimes 0·6. The intradermal tuberculin test was repeatedly negative. The serum bilirubin level was 0·5 per 100 ml., and the urinary urobilinogen was not increased. During an attack in March, 1952, there was 4% albumin in the urine and 10 to 40 red corpuscles per visual field. Blood pressure was normal, Rumpel-Leede's sign was negative, bleeding and coagulation times were normal, and no blood could be demonstrated in the stools. The platelet count was once 90,000, at other times normal.

The patient was treated with iron, folic acid and liver extract. In one of the crises blood transfusions only were given. The blood counts returned to normal in about four weeks irrespective of the mode of treatment. Each remission was followed by a relapse. The course of the attacks is shown in Fig. 1.

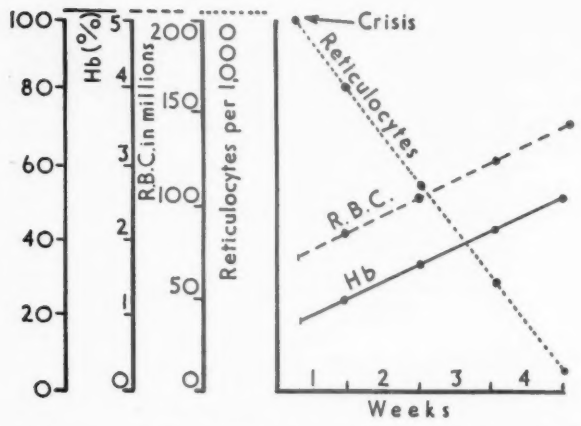

FIG. 1.—Diagram of the haematological response to treatment with iron, vitamin B and folic acid.

Indication for Splenectomy. The child was admitted to the Department three to four times a year with severe anaemia and in a grave state. The negative history, the absence of spherocytosis and the normal level of both bilirubin and urobilinogen were against familial haemolytic anaemia; acquired haemolytic anaemia could be excluded, since no autohaemolysin and agglutinin could be demonstrated. The negative radiological finding was assessed against essential pulmonary haemosiderosis.

The spleen was often hardly palpable; it extended in general by ½ to 1 cm. beyond the costal margin. It must, however, be emphasized that Wiseman and Doan (1942) observed hypersplenism without enlargement of the spleen. In view of the frequent, almost fatal relapses and the failure of the therapy and the fact that the bone marrow count and the reticulocyte count exceeded 200 per thousand cells, splenectomy still seemed justified and accordingly the spleen was removed by Prof. B. Molnar.

Course of the Disease after Splenectomy. The child supported the operation relatively well, but on the third day pneumonia developed. In spite of this blood counts showed a marked improvement (red cells, 3,710,000, white cells, 4,500 with 1 metamyelocyte, 23 young, 49 segmented neutrophils, 3 monocytes, 4 lymphocytes per 100 cells). There were 4% normoblasts and anisocytosis and polychromasia. Four weeks after the operation the child was discharged, apparently in good health. A blood count then gave 4 m. red cells and 72% Hb. Erythrocyte resistance was either normal or varied between 0·30 and 0·52 % NaCl.

Ten weeks after the operation the patient was brought back to the hospital in a bad condition developing after measles associated with pneumonia, from which time onwards he had frequently vomited and coughed. Clinical examination revealed pneumonia. The radiograph showed miliary tuberculosis. The tuberculin test was negative as before, but on account of the measles this could not be assessed against tuberculosis. No signs of tuberculosis were found either in the cerebrospinal fluid or by ophthalmological examination. The positive x-ray finding after measles had induced us to transfer the child to a tuberculosis ward of John's Hospital for streptomycin treatment. There a collapse-like state was once observed, when the child had tonsillitis accompanied by a temperature of 39° C. Within eight days the severe anaemia was under control. The radiograph did not show any change but the general state remained satisfactory.

When in March, 1953, the case was presented to the Section of Paediatrics with a diagnosis of hypersplenism, and it was pointed out that the primary or secondary character of the condition had not been diagnosed positively, Dr. I. Flesch suggested that the case might still be one of essential pulmonary haemosiderosis.

Laboratory Diagnosis of Essential Pulmonary Haemosiderosis. Certain points, however, were in favour of miliary tuberculosis: (1) the seemingly characteristic x-ray radiological finding, and (2) the recent measles. Against miliary tuberculosis was the fact that a tuberculin test could not have been negative with miliary tuberculosis except at the onset of the disease, soon after the measles. The fact that the Mantoux test remained negative in the subsequent months was a warning signal that the diagnosis of tuberculosis was erroneous.

It is characteristic of essential pulmonary haemosiderosis that macrophages containing haemosiderin are found in the alveoli and also the remnants of recent haemorrhage in the form of many red corpuscles. The alveolar walls and interalveolar septa are thickened, and there is an increased amount of reticulin and collagen fibres. The elastic fibres of the small and medium pulmonary vessels are swollen, brittle, hypoplastic and impregnated with iron. Up to the present, 'heart failure' cells in the sputum were considered of diagnostic value, such cells having been demonstrated in essential pulmonary haemosiderosis by Hanssen (1947), Wyllie, Sheldon, Bodian and Barlow (1948), King (1949) and Gellis, Reinhold and Green (1953). Our patient had no sputum. Blood in the faeces could not be demonstrated either before or after operation. No heart failure cells

were found in the gastric contents. Diagnostic lung puncture had not been tried. It had been applied in three cases of pulmonary haemosiderosis, but it involves a certain risk because of the nature of the disease. This is why a diagnostic procedure hitherto not applied in pulmonary haemosiderosis, exploratory thoracotomy with lung biopsy, was preferred. When we decided to resort to that procedure it was reassuring that, according to Bernatz and Clagett (1953), if the nature of a pulmonary lesion cannot be recognized with certainty and if the patient's life is in danger, thoracotomy has to be performed. The risk is slight, for Bernatz and Clagett have carried out exploratory thoracotomy with lung excision in 47 cases without any untoward results. On the strength of this experience, Dr. K. Joos carried out a lung biopsy.

According to the histological examination made by Dr. Schuler, of the First Institute of Pathological Anatomy and Cancer Research of Budapest Medical University, the alveoli were filled with mononuclear phagocytes containing iron (siderophages) and the interstices were somewhat thickened. The elastic system of the vessels was degenerated and impregnated with iron. The degenerating elastic fibres of the small vessels were phagocytosed by foreign-body giant cells. In some areas perivascular round-cell infiltration appeared.

The diagnosis was pulmonary haemosiderosis. If this is not consequent upon some disease of other organs or of the vessels, the case is one of essential pulmonary haemosiderosis.

Discussion

Effect of Splenectomy. The illness, from the first complaint to the operation, lasted 27 months, during which time the child was in a poor state of health. Seven times he was admitted in a grave state, and on each occasion he spent one to three months in hospital. During the six months after the operation the child had two attacks. In the interval the haemoglobin varied between 69 and 80%, and the red cell count between 3,000,000 and 4,200,000 per c.mm. The red cells did not respond to treatment with liver extract. It seemed instructive to study how far the course of the post-operative exacerbations differed from those before splenectomy. The first attack occurred on October 18, 1952, three months after the operation. It was preceded by measles and pneumonia. It was indicative of the seriousness of the crises that the up to then virtually negative radiograph revealed for the first time a marked change interpreted as typical of miliary tuberculosis (Fig. 2). In spite of the attack the haemoglobin varied between 54 and 63%, as against the 20% of the pre-operative crises. The red cell count varied from 3,340,000 to 2,890,000 per c.mm. while during the attacks before splenectomy it was frequently below 2,000,000 per c.mm.

The second crisis occurred on February 18, 1953,

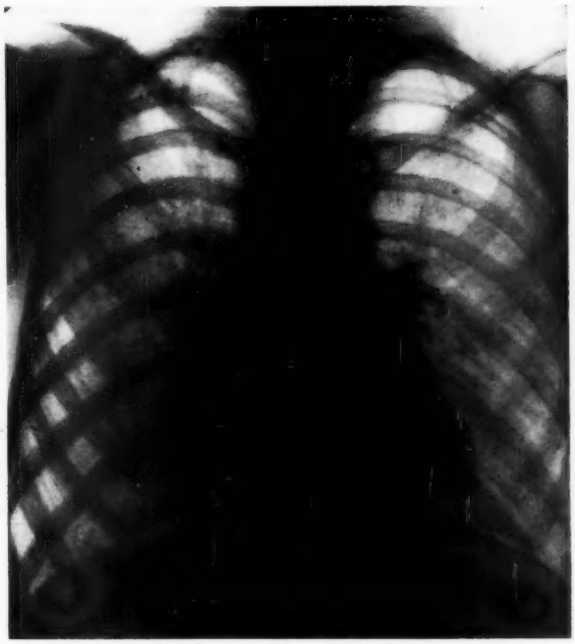

FIG. 2.—Radiograph of U. on October 27, 1952.

with follicular tonsillitis as the primary disease. At this time the child was in a state of collapse, with increasing dyspnoea, and a pulse rate of 160. The red blood cells decreased from 3,340,000 to 2,400,000 and the white cell count was 18,000 (150,000 thrombocytes). On February 22, 280 ml. of blood was transfused and by the next day the general state was considerably improved, with 70% Hb and 2,860,000 red cells. Eight days after the onset of the attack the red cells numbered 3,500,000, Hb was 70% and the platelet count was 210,000. Before splenectomy three to four weeks had been needed to cure the anaemia developing during an attack, but after splenectomy a sudden bout could be controlled in a single week. Blood counts in attacks before and after splenectomy are presented in Table 2.

The bone marrow yielded instructive data (Table 1). In the attacks before splenectomy marked hyperplastic erythropoiesis had been present with 147·6 erythroid to 100 myeloid cells. Immediately after the operation the hyperfunction ceased and only 22·2 erythroid elements were found per 100 myeloid ones. The number of reticulo-endothelial cells decreased from 6·8 to 0·8. In the first attack after splenectomy, in contrast to the previous episodes, a shift to the left in granulopoiesis presented itself. Increased erythropoiesis, anisocytosis, polychromasia, were again demonstrable. Basophilic stippling was present but the myeloid-

TABLE 1
BONE MARROW STUDIES

	Before Splenectomy (Oct. 19, 1951)	After Splenectomy		
		Aug. 4, 1952	Oct. 27, 1952	Nov. 5, 1953
Myeloblasts	0·2	0·6	0·6	0·6
Promyelocytes	4·4	6·0	7·0	5·1
Myelocytes	22·2	20·6	30·6	15·3
Metamyelocytes	20·0	17·2	29·6	20·9
Unsegmented neutrophils	19·6	17·6	15·0	25·1
Segmented neutrophils	7·6	17·8	2·7	17·1
Immature eosinophils	12·0	9·4	4·3	4·2
Mature eosinophils	3·6	3·4	1·0	0·3
Monocytes		0·2		
Lymphocytes	10·4	7·2	9·2	8·4
	100·0	100·0	100·0	100·0
Pronormoblasts	13·2	0·4	1·3	1·2
Macroblasts	23·6	1·8	3·6	3·0
Normoblasts	110·8	20·0	68·0	32·1
	147·6	22·2	72·9	36·3
Macrophages		0·2	0·2	
Lymphatic reticulum cells	3·2	0·2		1·2
Plasma-cellular cells	3·6	0·4	3·0	1·8
	6·8	0·8	3·2	3·0

erythroid ratio did not rise to above 100 to 72·9. At the same time the number of reticulocytes rose to 120 per 1,000 cells. On November 5, 1953, when for nine months no attack had been observed, bone marrow counts were normal, with 36·3 erythroid elements per 100 myeloid ones; anisocytosis and poikilocytosis were slight.

From February 20, 1953, to February 28, 1954, no exacerbation was observed. The child went to school, played football, was free of complaints. Despite the fact that the disease did not progress, a complete cure was not achieved, since the radiological finding, the clubbing of the fingers, the peculiar pinkish-blue tinge of the skin and the dyspnoea on stress have remained unchanged (Fig. 3).

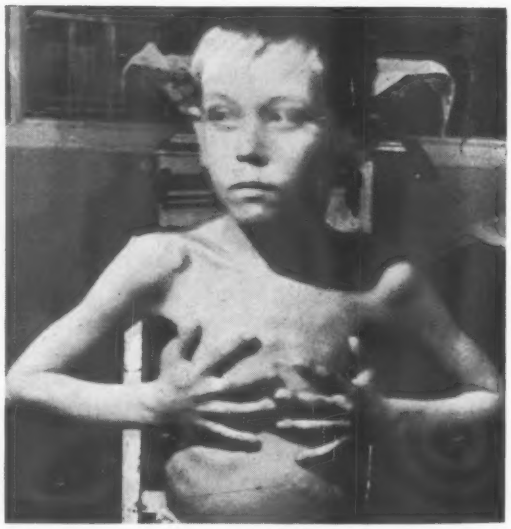

FIG. 3.—Patient's photograph.

Aetiology of Essential Pulmonary Haemosiderosis. Several theories concerning the aetiology of the disease have been put forward. Ceelen (1931) who

TABLE 2
CRISIS BLOOD COUNTS

	Before Splenectomy (1951)			After Splenectomy (1952)	
	Oct. 12	Oct. 29	Nov. 15	Oct. 23	Nov. 28
Haemoglobin (%)	22	43	52	63	70
Red cells (c.mm.)	1·9	2·6	3·2	3·3	4·2
White cells	9,100	8,300	5,700	17,200	28,000
Unsegmented neutrophils	9	4	5	3	6
Segmented neutrophils	52	54	43	63	63
Eosinophils	13	16	20	1	—
Basophils	1	—	—	2	—
Lymphocytes	18	23	28	30	27
Monocytes	7	3	4	1	4
Reticulocytes (per 1,000)	220	95	16	—	—

first described the condition, attributed it to a primary developmental abnormality of the elastic fibres in the lungs, the elastic fibres showing fragmentation. This led to stasis in the capillary vessels, and to the haemorrhages both massive and per diapedesim. The primary defect would amply explain the progress of the disease as a consequence of the repeated haemorrhages.

The elastic fibres become impregnated with iron pigment, but occasionally bundles of elastic fibres which are not impregnated with iron would prove (Flesch, Schuler and Szöke, 1953) that the primary change is the defect of the elastic fibres, and this is followed by the haemorrhages and the formation of haemosiderin. According to this concept, the lethal outcome cannot be averted, and the most one can achieve is to relieve the anaemia developing during the relapse. Nitschke (1944), in view of the accumulation of haemosiderin, considered essential pulmonary haemosiderosis to be a storage disease.

The changes described by Ceelen, provided that the disease ran a protracted course, were observed by all subsequent authors.

It is remarkable that in the case of Scheidegger and Dreyfus (1945), in which the first symptoms had occurred at the age of 3 months and death at 1 year, neither defective development nor fragmentation of the elastic fibres, the very changes considered characteristic of the disease, could be found in the lungs. Nancekievill (1949) reported a similar case in a girl of $2\frac{1}{2}$, in which hardly one and a half months elapsed between the onset of the symptoms and death, and in which a careful histological study could reveal no change in the elastic fibres. According to Nancekievill the so-called fragmentation of elastic fibres and the fibrotic thickening of the alveolar wall are, consequently, sequels rather than the cause of the disease. In the $3\frac{1}{2}$-year-old patient of Reye (1945) the disease lasted 11 months and an increase in the number of elastic fibres could be demonstrated.

The three cases cited make it questionable whether hypoplasia of pulmonary elastic fibres should be truly regarded a primary symptom, and whether it is a consequence of some structural defect in the lungs. Against that assumption are (1) the course of the disease in my patient with its periodical attacks, which are hardly consistent with the permanently extant anatomical lesion, and (2) the increase in number of eosinophils, a finding frequently associated with allergic phenomena. Third is the fact that after splenectomy the attacks decreased in frequency and later completely ceased. Similar observations have been reported by British and Portuguese authors. It is unlikely that splenectomy would have been capable of improving the state of the primarily defective pulmonary elastic fibres. What then might be the role of the spleen in the aetiology of the condition? Increased splenic activity, so-called hypersplenism, might cause a fall in the number of erythrocytes, either by inhibiting the bone marrow or by bringing about an increased destruction of red corpuscles. Inhibition of marrow activity was not present, since erythropoiesis was increased and the release of erythrocytes did not meet with obstacles. As to the second eventuality, in the removed spleen Malpighian follicles were normal but were fewer than usual and were irregularly situated. Some of these follicles were hyperplastic. The most characteristic feature under the microscope was a marked thickening of the usually delicate reticular basal tissue, which considerably exceeded in amount and took the place of the lymphatic substance. The lymphoid tissues were regular and stained adequately and there were relatively few erythrocytes between them. The number of eosinophils was, however, remarkably high, and these cells were scattered or in groups of eight to 10 in every field. No other kinds of cell occurred in the spleen, giant cells were not found, and there was no sign of increased erythrocyte phagocytosis (Dr. Vécsei). This finding corresponds to the so-called depressive or antihaemopoietic hypersplenism. In haemolytic hypersplenism, the considerable hyperaemia of the pulp, the swelling of the endothelial cells in the sinus, and eventually the presence of pigment macrophages are considered as typical. While in our case the number of Malpighian follicles was markedly reduced, Cordeiro (1952) observed in his patient a hypertrophy and hyperplasia of follicles, and emphasized that neither pulpar nor follicular fibrosis was present. In both cases splenectomy proved beneficial. It seems therefore probable that no increased destruction of red corpuscles ensued in the spleen.

If one wished to outline the aetiology of essential pulmonary haemosiderosis on the basis of the above data, taking into account both the clinical picture and the result of the splenectomy, the following concept appears justifiable. The spleen plays an important role in the origin of the condition, considering that after its removal the number of grave attacks decreased and none at all have occurred for a year. Paterson (1946), de Castro Freire and Cordeiro (1948) and Cordeiro (1952) have reported similar results. This, however, does not mean that the underlying factor is a simple hypersplenism in the old sense of the word; it seems probable that the disease is caused by some unknown sensitizing

agent eliciting auto-antibody formation. In the case of essential pulmonary haemosiderosis these antibodies occur in great quantity in the alveoli of the lungs. We believe that in essential pulmonary haemosiderosis the lung alveoli represent the shock tissue.

If on the impact of a fresh allergen an allergic reaction takes place in the pulmonary tissue sensitized in the above way, then in our opinion this will manifest itself in capillary dilatation, stasis, and an increase of permeability. As a consequence, a protein-rich exudate leaves the vessels, and diapedesic haemorrhages occur. In the present case the decreased resistance of erythrocytes has also contributed to the increase and to the intensity of the haemorrhage.

Wyllie *et al.* (1948) contributed valuable data to the assumption according to which in essential pulmonary haemosiderosis substances are produced which, as auto-agglutinins, viz. haemolysins, promote the increased destruction of erythrocytes. In one of their patients cold agglutinins against his own erythrocytes could be demonstrated in a titre of 1 to 10 million and against the cells of the O group in a dilution of 1 in 64. Wyllie *et al.* considered the high titre of cold agglutinins to be an antibody response to the destruction of erythrocytes in the child's lungs. In our opinion it is more probable that the agglutinins of high titre caused the lesion of the blood corpuscles and that the injured erythrocytes were more easily destroyed.

The fact that attacks occurred even after splenectomy may be explained in several ways. (1) An accessory spleen was left over. This could not be the case since later on the attacks stopped. (2) The spleen had no particular role in the condition except as part of the reticulo-endothelial system which continued to exert its effect after splenectomy. The fact that the bouts ceased favours the supposition that the spleen has an important function in the production of the sensitizing agent and its fixation. It probably also plays a role in the production of antibodies. On the strength of this concept, essential pulmonary haemosiderosis is an allergic disease and the mechanism of its origin is closely related to those of acquired haemolytic anaemia and idiopathic thrombocytopenic purpura.

Conclusions

This concept of the aetiology of essential pulmonary haemosiderosis leads to vitally important conclusions. In the first place it removes the condition from the list of the infallibly lethal diseases and declares it curable, substituting for the morphological explanation a functional one. On the basis of the old theory no search for an eliciting agent was needed, the anatomical lesion having been considered a basic feature of the disease, whereas today the investigation of the sensitizing agent has come to the fore.

Early diagnosis assumes a far greater importance, since it has become possible to anticipate complete regression, whereas in the case of a belated diagnosis, irreversible changes may have already occurred in the lungs. If the disease has lasted several years certain points in the history may easily escape due attention. Thus, in our case with periodical attacks, no attention was paid to the fact that a tuberculin-negative child had had a haemoptysis. On the strength of recent knowledge this point by itself would justify taking essential pulmonary haemosiderosis into account in the differential diagnosis. At the onset of the disease the chest radiograph may be entirely negative.

The absence of an enlarged spleen is no reason against splenectomy. For the time being this is the only curative procedure. It seems worth while to administer A.C.T.H. (Stefanini, Roy, Zannos and Dameshek, 1950) or cortisone before operation.

Further experience will show whether the beneficial effect of splenectomy will manifest itself in those forms of essential pulmonary haemosiderosis in which (*a*) heredity can be demonstrated, (*b*) the resistance of red blood corpuscles is not decreased, (*c*) no erythroid hyperplasia occurs in the bone marrow.

Summary

A case of essential pulmonary haemosiderosis diagnosed during life is described.

Diagnosis was made by thoracotomy.

As a therapeutic measure splenectomy was performed. Thereafter the disease ceased to progress and not a single attack associated with anaemia was observed for 12 months. This is the fourth case in the world literature improved in this way.

Essential pulmonary haemosiderosis is considered to be an immuno-allergic disease, caused by a still unknown sensitizing agent inducing the production of auto-antibodies. The antigen-antibody reaction causes in the lungs, as the shock organ, capillary dilatation, consequent stasis, diapedesis, rhexis, increased destruction of the injured red corpuscles and deposits of haemosiderin.

Early diagnosis must be aimed at, since in this way there is hope for complete restoration to health.

References

Bernatz, P. and Clagett, O. T. (1953). *J. Amer. med. Ass.*, **152**, 379.

Borsos-Nachtnebel, Ö. (1942). *Zbl. allg. Path. Anat.*, **79**, 174.

Castro Freire, L. de and Cordeiro, M. (1948). *Helv. paediat. Acta*, 3, 255.

Ceelen, W. (1931). In *Handbuch der spezielle pathologischen Anatomie und Histologie*, ed. F. Henke and O. Lubarsch, Bd. 3, t. 3. Berlin.

Cordeiro, M. (1952). *Helv. paediat. Acta.*, **7**, 501.

Ellman, P. and Gee, A. (1951). *Brit. med. J.*, **2**, 384.

Flesch, I., Schuler, D. and Szöke, G. (1953). *Gyermekgyógyászat*, 4, 300.

Gellis, S. S., Reinhold, J. L. D. and Green, S. (1953). *Amer. J. Dis. Child.*, **85**, 303.

Hanssen, P. (1947). *Acta. paediat., Uppsala*, **34**, 103.

King, A. B. (1949). *Proc. roy. Soc. Med.*, **42**, 87.

Nancekievill, L. (1949). *Brit. med. J.*, **1**, 431.

Nitschke, A. (1944). *Klin. Wschr.*, **23**, 348.

Paterson, D. (1946). *Proc. roy. Soc. Med.*, **39**, 131.

Reye, D. (1945). *Med. J. Aust.*, **1**. 35.

Scheidegger, S. and Dreyfus, A. (1945). *Ann. Paediat., Basel*, **165**, 2.

Stefanini, M., Roy, C. A., Zannos, L. and Dameshek, W. (1950). *J. Amer. med. Ass.*, **144**, 1372.

Waldenström, J. (1944). *Acta radiol., Stockh* , **25**, 149.

Walton, M. and Williams, A. (1951). *Brit. med J.*, **2**, 390.

Wiseman, B. and Doan, C. (1942). *Ann. intern. Med.*, **16**, 1097.

Wyllie, W., Sheldon, W., Bodian, M. and Barlow, A. (1948). *Quart. J. Med.*, **17**, 25.

PSEUDO-HYPOPARATHYROIDISM

A DESCRIPTION OF THREE CASES AND A CRITICAL APPRAISAL OF EARLIER ACCOUNTS OF THE DISEASE

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(RECEIVED FOR PUBLICATION APRIL 26, 1954)

The credit for recognizing that the term 'chronic idiopathic hypoparathyroidism' denotes at least two clinical entities belongs to Albright and his colleagues. In 1942 Albright, Burnett, Smith and Parson separated off a group of cases which they designated as 'pseudo-hypoparathyroidism', and they provided three illustrative case reports. In a second paper, in 1950, Elrick, Albright, Bartter, Forbes and Reeves defined this entity with greater precision, using data obtained from the study of 14 cases. These consisted of their own earlier three cases, and of four new ones of their own, as well as of those published by Sprague, Haines and Power (1945) and by Peterman and Garvey (1949). Five other unpublished cases which are referred to but of which the details are not provided in full make up the total of 14.

Pseudo-hypoparathyroid patients, according to these writers, are to be distinguished from other cases of chronic idiopathic tetany (and henceforward in this article this second group will be labelled 'spontaneous hypoparathyroidism') by the following characteristics.

(1) Clinically and biochemically they appear to conform to the pattern of parathyroid insufficiency. Drake, Albright, Bauer and Castleman (1939) regard a low serum calcium level with a high serum phosphorus level, unaccompanied by generalized bone disease, but with normal renal function and fat absorption, as the essentials of this diagnosis. Despite these findings, cases of pseudo-hypoparathyroidism show little or no response to parathyroid hormone either clinically or chemically, and some cases do not react in the normal way to A.T.10 (dihydrotachysterol) either (cf. Fig. 1).

(2) A typical physique is described, the components of which are a round face, shortness of stature, and a stocky or thick-set build.

(3) Changes in the shape of the metacarpal bones, less often of the metatarsals and phalanges as well, are frequently present. Metacarpals 1, 4 and 5 are chiefly affected, and metacarpal 2 only rarely, whereas metatarsals 1 and 5 are the ones usually involved. These bones are abnormally short, often wider than normal, and sometimes their epiphyses invaginate the diaphyses because of inequality in rates of growth. In one case (that of Dr. J. Browne) premature closure of the epiphyses at the elbow, bowing of the legs and exostosis formation were present, and early closure of epiphyses was held to account for short stature in other cases. In short, an atypical chondrodystrophy is often associated with this syndrome.

(4) Subcutaneous calcification is present in many (10 of the 14 cases listed) and is usually associated with brachydactyly, inasmuch as only one case exhibited calcification without metacarpal changes. The calcification is generally in the neighbourhood of joints, especially of those in the hands and feet, but may be present in other sites. In some cases, as has been proved by biopsy, actual bone formation occurs.

(5) In three cases biopsies were carried out on the parathyroid glands. In two of these hyperplasia of the removed gland was found, and in the third a normal histology. (This case, however, had been treated for one month with A.T.10 before the biopsy was done.) From these findings and the observed insensitivity to parathyroid hormone the authors deduce that parathyroid hormone is being secreted by the glands, and that the metabolic error lies in the end-organ which is failing to respond to it. The original (1942) paper was sub-titled 'An Example of the Seabright Bantam Syndrome', thereby drawing an analogy to the Seabright Bantam cockerel which displays female plumage in spite of having androgenic hormone in the circulation, presumably because the end-organs fail to respond to the hormone. The beardless face of the American Indian, and the pitressin-resistant case of diabetes

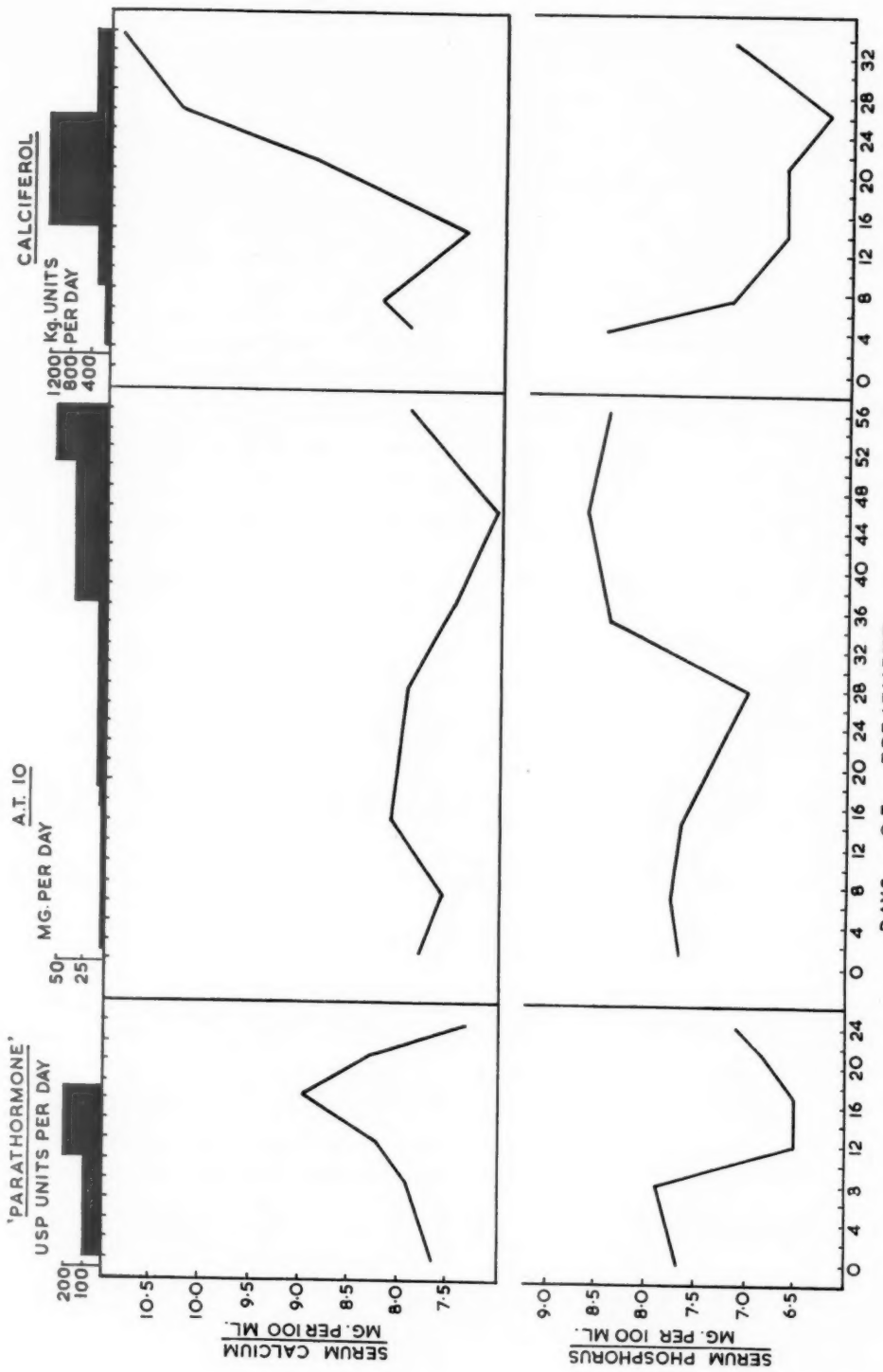

FIG. 1.—The serum calcium and serum phosphorus levels of Case 3 during treatment with 'parathormone', A.T.10 and 'calciferol'.

insipidus are other examples of end-organ unresponsiveness. However, as Alexander and Tucker (1949) point out, the comparison with the Seabright Bantam is unsatisfactory because Morgan's (1915) paper that describes the reactions of this bird reveals also that castration would restore the plumage to that of a normal male. Some more complex explanation than end-organ failure is therefore required. Perhaps for this reason Albright and his colleagues no longer designate pseudo-hypoparathyroidism as the Seabright Bantam syndrome after their first reference to the term (Albright *et al.*, 1942). Nevertheless so colourful an association with a disease is not easily left behind, and it is still to be found in many textbook accounts of the condition.

Elrick *et al.* (1950) encountered the abnormality in two sets of identical twins, and in a mother and son, and suggested that there is an hereditary factor in the condition. They also drew attention to the low intelligence of several of their patients, presumed not to be a consequence of convulsions because one who was retarded had had no fits.

The authors conclude that the condition involves three disturbances, each of which is independent of the other two and can lead therefore to the following abnormalities, which may occur in any combination: (*a*) Disturbance of the parathyroid end-organ; (*b*) dyschondroplasia; (*c*) a propensity to form bone in subcutaneous tissues. When the second and third features are present without the first, tetany will of course be absent and serum calcium and phosphorus values normal. Such a case (tortuously labelled pseudo-pseudohypoparathyroidism!) was described by Albright, Forbes and Henneman (1952) in a Colombian girl who possessed all the physical features of pseudo-hypoparathyroidism except for hypocalcaemia, but interestingly enough is not related to have been mentally retarded. These authors very plausibly suggest that pseudo-hypoparathyroidism arises from the mutation of a gene which controls several traits, and offer as clinical parallels the syndromes of ovarian agenesis and of polyostotic fibrous dysplasia, in each of which an endocrine disorder is accompanied by several apparently unrelated abnormalities. It is now our intention to discuss in some detail the diagnostic criteria which have just been outlined.

Insensitivity to Parathyroid Hormone

It is of especial interest to observe by what standards the authors judge insensitivity to injected parathyroid hormone. Two of the cases in the 1942 paper were submitted to very large doses of parathyroid hormone (7,400 U.S.P. units in 12 days and 1,700 U.S.P. units in five days respectively) with no effect on serum calcium or phosphorus levels. Both these patients responded to A.T.10 with a rise of serum calcium, but the large dose of 25 mg. daily was necessary.

Ellsworth-Howard Test. In the other cases sensitivity to the hormone was assessed by means of the Ellsworth-Howard test (Ellsworth and Howard, 1934). This is a test which measures the power of an intravenous dose of parathyroid hormone to increase the renal clearance of phosphorus, and is simply performed by collecting hourly urine samples before and after an intravenous dose of 200 U.S.P. units (40 B.P.C. units) of parathyroid hormone, and comparing the subsequent urinary phosphorus excretion with the pre-injection levels. The originators of the test found that in normal subjects a two- or three-fold increase in phosphorus excretion was regularly obtained, often though not always accompanied by a diuresis, and that this rise occurred within the first three hours after the injection. When patients suffering from spontaneous or post-operative hypoparathyroidism were tested in this way an exaggerated response was obtained, the phosphorus clearance increasing by 10 or more times over the resting level. This enhanced response has been demonstrated in parathyroidectomized experimental animals, and in human parathyroid deprivation due either to thyroidectomy or to spontaneous deficiency by a number of other workers (Albright and Ellsworth, 1929; Emerson, Walsh and Howard, 1941; Berezin and Stein, 1948; Medill, 1951).

Albright and his colleagues were able to confirm Ellsworth and Howard's results on normal individuals, but when the Ellsworth-Howard test was used on their cases of pseudo-hypoparathyroidism it was found that different results were obtained (Elrick *et al.*, 1950). In three cases there was no response at all, although to one of these more than double the normal test dose of parathyroid hormone had been given. Repeated tests on the other two confirmed that an effect on phosphorus clearance was absent. In a fourth and fifth case, however, some response was obtained, though in the opinion of the authors there was a reduced sensitivity. 'Resistance to extract of parathyroid need not be complete', they remark, 'and the Ellsworth-Howard test alone may not be relied upon to distinguish between the two diseases,' namely pseudo- and spontaneous hypoparathyroidism. Writing at about the same time, however, Reifenstein (1950) stated that 'patients with pseudo-hypoparathyroidism may exhibit a two-fold increase in urinary phosphate

excretion, while normal subjects show a five- or six-fold increase, and patients with chronic or post-operative hypoparathyroidism show a ten-fold increase or greater'.

More recently, several published accounts reveal difficulties in reproducing the results of Ellsworth and Howard (1934) and Albright *et al.* (1942) in normal subjects. For example, Reynolds, Jacobson, Edmondson, Martin and Nelson (1952), in presenting a case of pseudo-hypoparathyroidism, admit that 'we have not obtained as marked a phosphorus diuresis as did the authors of the test, either in hypoparathyroid subjects or in normals, though two different brands and several batches of parathyroid hormone have been employed'. Dent (1953) performed the Ellsworth-Howard test on 15 normal people and found that there was hardly any increase in phosphorus excretion in the urine, in spite of the effectiveness of the parathyroid preparation in raising blood calcium levels in surgical hypoparathyroidism. He suggested that in modern preparations, which are assayed on their calcium-raising power, the phosphorus excretion effect is negligible. Milne (1951), however, although his results in normal subjects were much the same as Dent's, found that the hormone was able in the same dosage to produce a two- or three-fold increase in urinary phosphorus excretion in patients with spontaneous hypoparathyroidism. He concluded '. . . that the renal action of parathyroid hormone is maximal in hypoparathyroid states, but is already approaching its maximum in normals'.

Whatever the explanation, it is clear from these and from our own experience, which is described below, that the Ellsworth-Howard test does on many occasions fail to provoke phosphorus diuresis even in normal people. There is so far no great volume of evidence to contradict the impression that

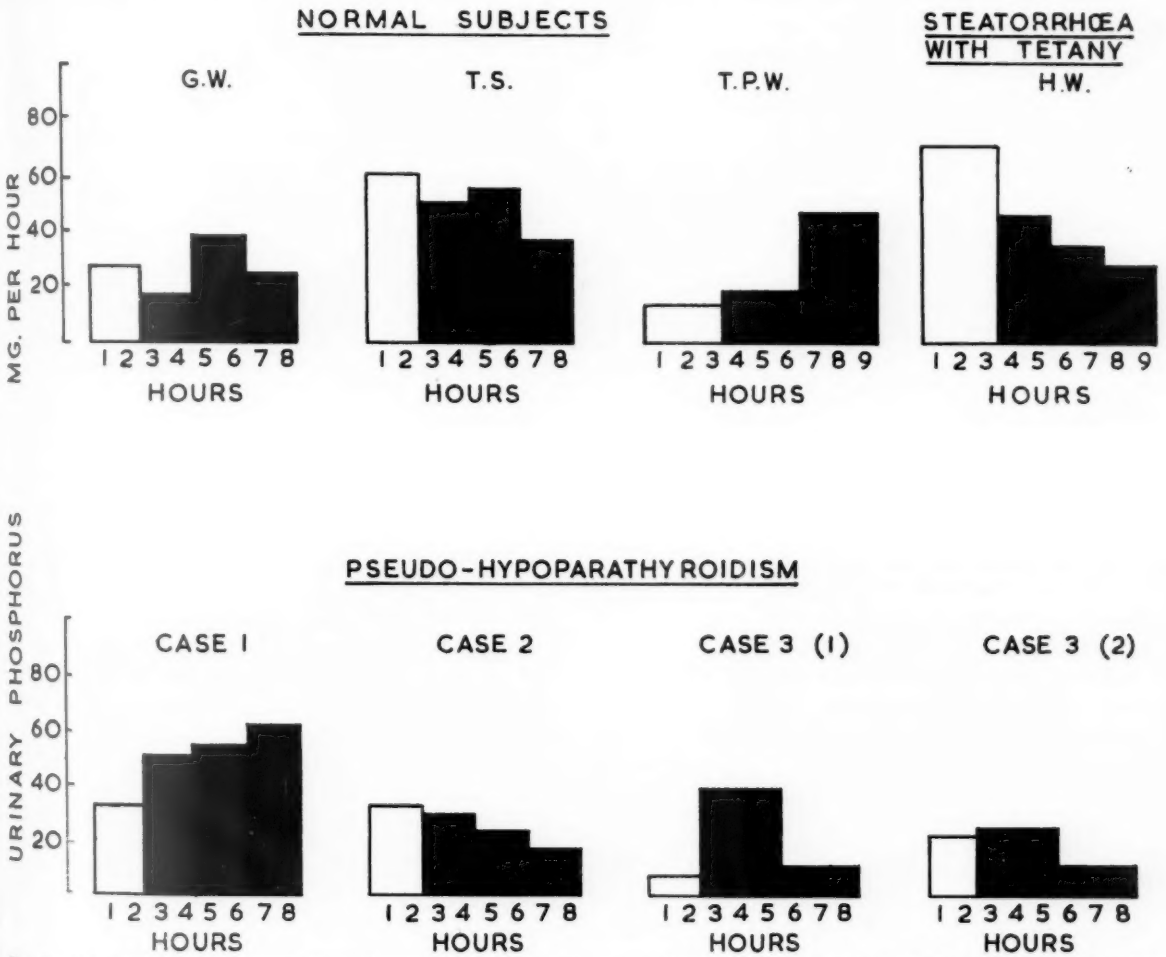

FIG. 2.—The results of the Ellsworth-Howard tests. Urinary phosphorus excretion before and (shaded areas) after infection of 200 U.S.P. units of 'parathormone' intravenously.

spontaneous and surgical hypoparathyroid patients always respond, but this test has been used in too few of the reported cases of spontaneous hypoparathyroidism for it to be looked upon as an invariable mode of reaction in those cases. Simpson (1953) reported a child with what is almost certainly spontaneous hypoparathyroidism, and in whom a negligible response to the Ellsworth-Howard test was obtained, while Dent (1953) in three cases of post-thyroidectomy tetany found no response to an Ellsworth-Howard test in one, and a comparatively slight rise in urinary phosphorus in the other two.

Nevertheless the test has been much employed in the diagnosis of pseudo-hypoparathyroidism by writers after Elrick *et al.* (1950), and in some of these it is the main support of the diagnosis.

Trial of Intramuscular Parathyroid Hormone. A normal person responds to moderate doses of parathyroid hormone by a slight but definite rise in the serum calcium level (Aub, 1935; Dent, 1953). There is a great deal of individual variation in the readiness with which this response is evoked. Hypoparathyroid patients react to smaller doses with a greater rise in calcium level, but in some of these after weeks or months sensitivity lessens and progressively larger doses are necessary to achieve an effect, which may ultimately be lost altogether (Thorpe and Handley, 1929; Hunter, 1931; Aub, 1935; MacBryde, 1938; Pope and Aub, 1944). If a hypoparathyroid patient who has not received previous injections of parathyroid hormone does not produce a significant rise in serum calcium in response to a series of parathyroid hormone injections in large dosage, it is very remarkable, and separates such a case from the ordinary patient with parathyroid deficiency.

Besides pseudo-hypoparathyroidism, there are other possible reasons for such a lack of response. In the first place, after surgical removal of a parathyroid adenoma very severe tetany may ensue, which parathyroid hormone is powerless to control (Albright and Reifenstein, 1948).

Then, in certain cases of steatorrhoea with tetany parathyroid hormone seems to be ineffective, as in the published case of Lowe, Ellinger, Wright and Stauffer (1950). In another case of steatorrhoea with tetany, for details of which we are indebted to Dr. A. I. Cheyne and whose clinical features are summarized in the appendix, a similar failure to respond to the hormone was observed. In this instance not only did an Ellsworth-Howard test give a negative result, but after four days of 150 U.S.P. units 'parathormone' daily there was no significant change in his low serum calcium and high phosphorus levels. Yet another case of steatorrhoea which failed to react to parathyroid hormone is known to us (Gillam and Morton, 1953).

Thirdly, Moehlig and Steinbach (1954) describe a patient with post-thyroidectomy tetany who became completely unresponsive to anti-tetanic drugs, including parathyroid hormone and dihydrotachysterol, while under treatment for another condition with cortisone. When cortisone was withdrawn, the tetany was again easily controlled.

Nevertheless, in spite of these limitations, it is a pity that this simple test has not been used more often (as it was by Albright *et al.*, 1942; Cases 1 and 3) for the diagnosis of pseudo-hypoparathyroidism in preference to the less reliable Ellsworth-Howard test. It is true that although brisk responses to parathyroid hormone have been obtained in many cases of spontaneous hypoparathyroidism (Liu, 1928; Albright and Ellsworth, 1929; Thorpe and Handley, 1929; Leopold and Jonas, 1932; Cantarow, 1932; Goerner and Samuelsen, 1934; Humphreys, 1939; Cantarow, Stewart and Morgan, 1939; Franco, 1940; Lachmann, 1941; Sutphin, Albright and McCune, 1943; Leonard, 1946), one cannot safely declare that all would respond in this way, and there are many instances in the literature of cases that have not been tried with this treatment. With present knowledge, it seems fair to assert that if a patient with idiopathic hypoparathyroidism, who has never previously received parathyroid hormone, fails to achieve normal serum calcium values after a week of injections of a potent preparation of the hormone in a dose of at least 200 U.S.P. units (40 B.P.C. units) daily, then it is not a case of spontaneous hypoparathyroidism and, if fat absorption is normal, may be diagnosed as pseudo-hypoparathyroidism. Where, in reported cases, an inadequate response to parathyroid has been encountered, there is the possibility not only that the case may be a spontaneous one which is unaccountably inert, but also that the case is in reality one of pseudo-hypoparathyroidism (e.g. cases reported by Martin and Bourdillon, 1940; Jordan and Kelsall, 1951). Without collateral evidence of other kinds it is therefore difficult to distinguish with absolute certainty on the basis of parathyroid hormone therapy between the two clinical entities. This fact has been recognized by a number of continental authors, who have questioned the existence of pseudo-hypoparathyroidism, believing the anomalous hormonal response to be explicable in terms of variable potency of commercial products and the latitude of individual responses (Gsell, 1950; Schüpbach and Courvoisier, 1949; Martin, Guye, Babel and Courvoisier, 1952; Martin, 1953).

The Parathyroid Glands

Little information has so far been collected about the appearance of the parathyroid glands in various states of hypoparathyroidism. Aplasia of the parathyroid glands is a very rare congenital malformation and is accompanied by other severe congenital defects incompatible with life (Drake *et al.*, 1939; Selye, 1949). In all reports of absence of the parathyroid glands it is important to be sure that the cadaver was examined carefully from the mediastinum upward well into the neck, because of uncertainty of the anatomical position of these glands (Morgan, 1936). A few reports from the continental literature of patients of various ages in whom no parathyroid glands were found after death are cited by Lachmann (1941). Some of these had had tetany during life, but the detail with which the glands were searched for is not recorded. The same limitation applies to the instances, also cited by Lachmann, in which impetigo herpetiformis of Hebra, a recognized association with chronic tetany (Simpson, 1954), had been present during life and in which absence of the parathyroid glands was reported at necropsy.

Undoubted cases of spontaneous hypoparathyroidism which have been examined after death include a girl of 11 years who also had Addison's disease (Leonard, 1946). This patient had given a satisfactory therapeutic response to parathyroid hormone, and at necropsy no parathyroid tissue was to be found nor any adrenal cortex. Drake *et al.* (1939) reported a boy of 10 years of age, with spontaneous hypoparathyroidism, who died of staphylococcal septicaemia. Information is not provided about the response obtained during life to parathyroid hormone in this case. At necropsy the parathyroid glands were found to be of normal size and encapsulated, but under the microscope they were seen to consist, apart from a few scattered chief cells, entirely of fat. Cantarow *et al.* (1939) recount the case of a 12-year-old Irish girl who for six years was treated for her spontaneous tetany with daily or alternate daily injections of parathyroid extract, with benefit throughout. She died of an unexplained haemorrhagic illness and, in spite of a thorough examination from the mediastinum upwards, no parathyroid tissue was found at necropsy. In this case the effect of the long administration of hormone upon any glandular tissue present at the onset of the disease must be assessed. A most interesting report is that by Eaton, Camp and Love (1939). These authors report a man, 22 years of age (their Case 1), who had suffered from attacks of painful clenching of the hands and flexion of the elbows from the age of 8, and in whom at 14 years generalized convulsions began. He also developed bilateral cataracts, lost his hair, suffered from increasing slowness and mental dulling, as well as from a chronic thrush infection of the mouth, and showed the characteristic symmetrical calcification of the basal ganglia associated with hypoparathyroidism. One observation of serum calcium at another hospital recorded a level of 11·9 mg. per 100 ml. This was not repeated, and Chvostek and Trousseau signs were not looked for. The patient had headaches and papilloedema, for which he had a craniotomy with negative findings. He died post-operatively of bronchopneumonia. Apart from a small (12 mm. diameter) cyst of the septum pellucidum, calcification was the only intracranial abnormality found at necropsy. Cystitis and oesophagitis were present. The parathyroid glands grossly and microscopically were normal. Despite the single serum calcium observation there are very strong grounds for considering this as a case of spontaneous hypoparathyroidism, and the interest of the parathyroid findings needs no emphasis therefore. Apart from the more obvious associations with chronic tetany that are present in this case history, thrush infection has been repeatedly described in hypoparathyroidism (Thorpe and Handley, 1929; Sutphin *et al.*, 1943; Simpson, 1954) and headaches and papilloedema from the same cause that can simulate a cerebral tumour are well recognized (Barr, MacBryde and Sanders, 1938; Levy, 1947; Grant, 1953).

Necropsy reports are not available for published cases of pseudo-hypoparathyroidism, though one of Lachmann's (1941) cases (No. 58) was almost certainly suffering from this disease. It is disappointing to find the post-mortem findings dismissed with the remark that 'autopsy revealed no abnormalities of interest in this connection' (i.e. chronic tetany).

Against this background we must consider the experience of Albright and his colleagues (1942 and 1952) with parathyroid biopsy in three cases of pseudo-hypoparathyroidism. Only one of these exhibited ectopic calcification or brachydactyly, and the only published information about the response to parathyroid hormone in another is derived from the results of an Ellsworth-Howard test. In the case with hand changes and calcification a normal gland structure was detected; in the other two the glands were reported to show hyperplasia.

Parathyroid biopsy has not been attempted in other cases (with the exception of our Case 3, reported below, where the results were inconclusive), and the method does not lend itself for use as a diagnostic test. The American observations require

to be extended. Quite apart from the gross structure of the gland, one must feel hesitation in interpreting histology in terms of function: hyperplasia need not imply hyperfunction nor normal histology a normally acting gland. A comparison with the diabetic pancreas is invited, and with the islet cell hyperplasia, which is often seen in haemolytic disease of the newborn, in which evidence of hyperinsulinism is wanting. Again, Eaton's report of a normal-appearing gland in a probable case of spontaneous hypoparathyroidism challenges the validity of this test as a criterion of diagnosis, especially in view of the paucity of knowledge about the parathyroid gland in cases of spontaneous deficiency.

Physique

It is unwise to seek conclusive support for a diagnosis in body build. Roundness of the face, though real enough in many cases, is not a sufficiently objective quality to serve as a basis of distinction, and this has been remarked upon by Reynolds *et al.* (1952). Nor is shortness of stature confined to cases of pseudo-hypoparathyroidism. Lachmann (1941) records that many of his 22 Danish cases of chronic idiopathic tetany were very well below the average height, and it is unlikely that the pseudo-hypoparathyroid cases in the series are entirely responsible, inasmuch as they are so much rarer than cases of spontaneous hypoparathyroidism. There have been other reports of patients responsive to parathyroid hormone who have been of short stature (Emerson *et al.*, 1941 (Case 1); McQuarrie, Hansen and Ziegler 1941). Stockiness is another rather subjective description; spontaneous cases seem to have been of any build, spare as were the cases of Brimblecombe (1949) and Salvesen (1930), or obese as were those of Mortell (1946), Lachmann (1941, Case No. 67) and Simpson (1952). Any effect of chronic hypocalcaemia on physique is likely to be more evident if the disease is present early, and the preponderance of dwarfism among pseudo-hypoparathyroid cases may be in part a reflection of the fact that in them the disorder is probably present from birth.

Mental Condition

In the histories of cases of chronic tetany it is difficult to decide whether mental infirmity, if present, developed before or after hypocalcaemia. One knows that a progressive dementia may set in after prolonged hypoparathyroidism of whatever cause (Simpson, 1952; Sugar, 1953), and so one must seek for cases of spontaneous hypoparathyroidism with reduced intelligence in childhood if a valid comparison is to be made, for many pseudo-hypoparathyroid cases are already recorded as defective at an early age. Examples of backwardness in young people with spontaneous hypoparathyroidism are to be found in the reports of Mortell (1946), Simpson (1952), Eaton and Haines (1939), Eaton *et al.* (1939) and Barr *et al.* (1938). Some of these were, perhaps, suffering from pseudo-hypoparathyroidism. Mental capacity, nevertheless, seems an unsound means of diagnostic differentiation.

Family History

Spontaneous hypoparathyroidism very seldom develops in more than one member of a family, and we have found in the literature only one example, namely the remarkable Italian family reported by Sutphin *et al.* (1943) in which three siblings suffered from the disease. This well-documented instance, however, eliminates family history as a perfect criterion for distinguishing between spontaneous and pseudo-hypoparathyroidism.

In addition to the three examples of family incidence in cases labelled as pseudo-hypoparathyroidism by Elrick *et al.* (1950), none of which for reasons stated elsewhere in this paper are included in the group of 27 cases which we have analysed below, there is some further evidence of a family tendency to the disorder. Thus, Lachmann (1941) reports an interesting family of five in which two sisters and a brother were affected, and probably also another sister (Cases 57, 58 and 59 of Lachmann). The remaining brother appeared to be unaffected. Selye (1949) reports a mother and child with the disease, Uhlemann (1950) found the disease in two sisters, and the sister of Azerad, Gatha and Raverdy's (1953) patient was also probably affected. All of these cases showed changes in the metacarpal bones, and we accept them as proven cases of pseudo-hypoparathyroidism.

There are objections, then, as we have seen, to accepting conventional methods of measuring the response to parathyroid hormone, or the results of parathyroid biopsy, or a special physical or mental constitution as diagnostic of pseudo-hypoparathyroidism. To the first the objection is the difficulty in interpretation, to the second that knowledge is inadequate, and to the third that overlap with findings in spontaneous hypoparathyroidism exists.

Bone Changes and Subcutaneous Calcification

No such criticism can be levelled at the remaining two criteria put forward by Elrick *et al.* (1950), namely chondrodystrophy mainly involving metacarpal and metatarsal bones and ectopic calcification. Wherever either of these have been observed

the case has conformed in other ways to the type described by Albright, and no instance of a satisfactory therapeutic reaction to parathyroid hormone is to be found among such cases. That reported by Cantor and Scott (1942) in whom there were 'several minute areas of calcification in the soft tissues of the neck' may be disregarded, as it was otherwise typical of spontaneous hypoparathroidism, and the calcium may well have been the relic of healed tuberculous lymph nodes. Other than this there are no reports of soft tissue calcification in parathyroid-hormone-sensitive cases. Intracranial calcification, common to all forms of chronic tetany (Camp, 1947; Siglin, Eaton, Camp and Haines, 1947), is of course excepted.

In collecting cases of pseudo-hypoparathyroidism from the literature, therefore, we have looked upon chronic tetany, together with brachydactyly and the characteristic metacarpal or metatarsal radiological changes, or with ectopic calcification or bone formation, as indisputable proof of the condition. Twenty-three cases of this kind have been discovered. This is not the total number, as it does not include the five unpublished cases alluded to by Elrick *et al.* (1950), about which only a few details are available, but otherwise the literature up to the end of 1953 has been fairly fully covered. In addition we present three new cases of our own, and one unpublished case is included for details of which we are indebted to Dr. W. W. Payne (1953). The clinical features of these 27 cases have been collectively studied, and some observations about them follow. Only 14 of them were published as cases of pseudo-hypoparathyroidism (Albright *et al.*, 1942, two cases; Sprague *et al.*, 1945, one case; Peterman and Garvey, 1949, one case; Selye, 1949, two cases; Schüpbach and Courvoisier, 1949, one case; Elrick *et al.*, 1950, one case; Alexander and Tucker, 1949, one case; Bakwin, Gorman and Ziegra, 1950, one case; Bishop and de Mowbray, 1951, one case; Reynolds *et al.*, 1952, one case; Bille, 1952, one case; and Azerad *et al.*, 1953, one case). The other cases were those of Himsworth and Maizels (1940), reported as congenital thyroid and parathyroid deficiency; Lachmann's (1941) three cases, Nos. 57, 58 and 59, reported as idiopathic hypoparathyroidism; of Richardson (1946), reported as chronic idiopathic hypoparathyroidism; of Scott and Temple (1949), reported as osteoma cutis; of Gsell (1950), reported as chronic idiopathic tetany; and of Uhlemann (1950), two cases, reported as familial idiopathic tetany.

Brief summaries of these cases are to be found in the appendix to this paper.

Details of our own cases now follow.

Case 1. R.V.B., aged 23 (date of birth February 14, 1930), an English male, was the only child of an unmarried woman living in poor surroundings. Details of the father are lacking, but the mother is said to be normal. The patient is said to have been normal until 6 years old, when he entered school and was discovered to be backward. In 1937, aged 7, he was admitted to a London hospital because of obesity and 'attacks'. Positive signs then were obesity, mental dullness and undescended testicles. The serum calcium level was 7·6 mg. per 100 ml. and serum phosphorus 3·7 mg. per 100 ml. The diagnosis was idiopathic tetany. The patient was readmitted in the following year, and diagnosed as calcinosis, for plaques of calcium had appeared on the face, hands, abdomen and ears. An ear tophus consisted of calcium phosphate with organic protein. He made little progress at school. On leaving he worked for a short time as a manual labourer, but in 1946 he was certified as a mental defective and admitted to a suitable hospital in Norfolk. Since admission there he had had two episodes which might have been convulsions or else attacks of tetany. During a period at home on licence he committed a sexual assault on a 4-year-old girl. He was admitted to our care for observation on November 25, 1953.

He was childish, amiable and lacking in iniative, and spoke slowly in a monotone. His face was expressionless, round, and with few associated movements. His physique was muscular but not obese (Fig. 3). He walked bent a little forward with a shuffling gait. His height was 5 ft., weight 77 lb., span 58 in., symphysis to soles 30½ in. and symphysis to vertex 29½ in. The hands showed unusually short thumbs. The feet showed shortening of toes 1, 4 and 5 (Fig. 4).

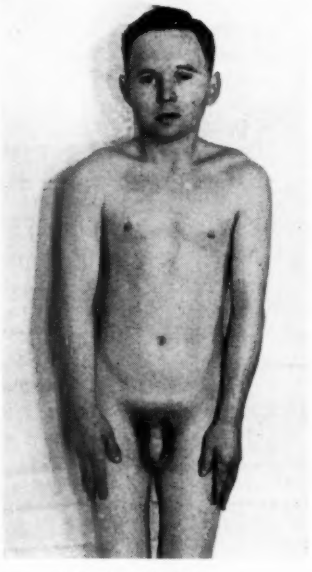

FIG. 3.—Case 1.

Acuity of vision was fair. Coarse radial opacities were visible in the periphery of the lenses. The ocular fundi were normal.

The nails were normal on the hands, thickened on the feet.

A number of small sessile papillomata were seen in the upper part of the body. Numerous flat reddish-brown naevi were scattered about the body. A biopsy of one of these showed a simple naevus pigmentosus of intradermal type. Patches of symmetrical eczema on both hands were said to have been present for one year. Numerous subcutaneous nodules of calcium hardness, the largest an irregular plaque over the left zygoma, were

felt. Palpable nodules were also found at the back of the neck, on the dorsa of the arms and on the hands and feet. The Chvostek sign was positive, and the Trousseau sign negative.

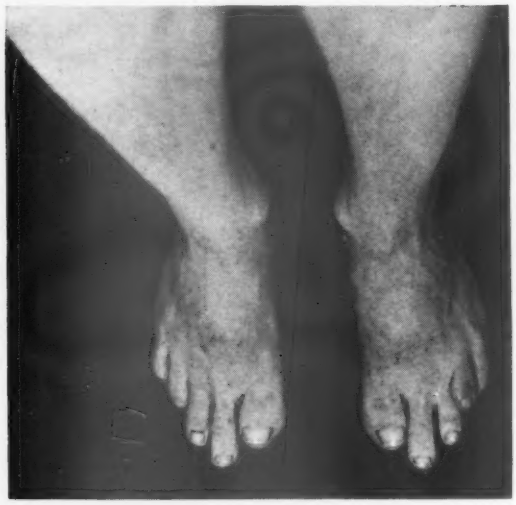

FIG. 4.—Feet of Case 1.

He was edentulous, and the hair was normal. Blood pressure was normal.

INVESTIGATIONS. Serum calcium level was 7·6 mg. per 100 ml., serum phosphorus 5·7 mg. per 100 ml., serum alkaline phosphatase 7·3 K-A units per 100 ml. The Sulkowitch test was negative, otherwise no urinary abnormality, and the urinary 17-ketosteroid excretion 6·2 mg. a day. The serum sodium, potassium, chloride, urea and alkali reserve were normal. An electrocardiogram was normal.

X-RAY EXAMINATION. This showed general osteoporosis of the skeleton with loose texture, and extensive calcification of the soft tissues, much of it subcutaneous, especially marked in the hands and feet and around most of the large joints.

The spine showed slight osteoporotic flattening and concavity, with calcification of short anterior ligaments in the mid-dorsal region.

Extensive fairly symmetrical calcification in the region of the basal ganglia, several unerupted molar teeth in the upper and lower jaws, soft-tissue calcium plaques below the occipital protuberance and left fronto-temporal region were all seen in the skull plates.

Right humerus varus with osteo-arthritis and capsular calcification was seen.

Very marked osteoporosis of the pelvis was observed. There were small subcutaneous calcium deposits around the knees, and an exostosis of the right upper fibula.

The first and right fifth metacarpals of the hands were strikingly shortened with very loose texture in the fifth metacarpals. Subcutaneous calcification was extensive (Fig. 5).

The first metatarsals and phalanges of the feet were short and thick, and the left fourth and right fourth and fifth metatarsals were strikingly shortened. Extensive subcutaneous calcification was seen.

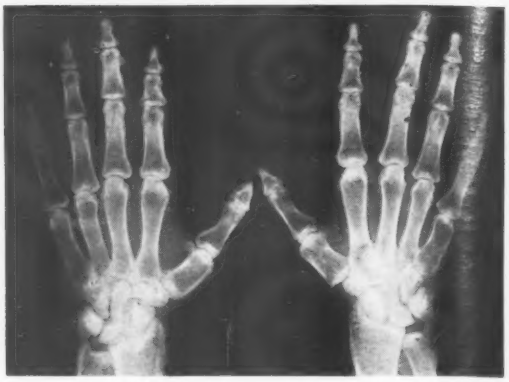

FIG. 5.—Case 1, radiograph of hands.

ELECTRO-ENCEPHALOGRAM. The record was moderately abnormal with evidence of failure of maturation, but none of any tendency to seizures.

MENTAL STATE. His intelligence quotient was 52 on the Terman-Merrill Form L.

ELLSWORTH-HOWARD TEST. See Fig. 2 and the subsequent discussion.

RESPONSE TO PARATHYROID HORMONE. 'Parathormone' (Lilly) was injected intramuscularly for seven days in a single dose of 200 U.S.P. units per day. The Chvostek sign was present throughout. The serum calcium level before was 7·6 mg. per 100 ml. and after 7·5 mg. per 100 ml.; serum phosphorus level before, 5·7 mg. per 100 ml. and after, 4·9 mg. per 100 ml.

Case 2. V.C.E., aged 24 (date of birth November 16, 1929), was a Welsh girl. Comparatively little is known of her early history, as her mother died when she was 3 years old, and she was brought up in an orphanage. She had an unexplained illness in infancy, after which she developed fits. Because of backwardness and timidity she did not go to school until very late. She was certified as a mental defective in 1947, at the age of 17. Since then she has been in a mental defective hospital in Glamorgan. She was admitted to our unit for investigation on January 11, 1954.

In the hospital for mental defectives she had shown herself as a pleasant, smiling person, quiet and affectionate, but timid and easily affected by nervous influences. Since admission she had been subject to recurrent vomiting attacks which lasted for several days and seemed to be excited by nervous causes, during which manifest tetany had been observed. Once hemitetany was seen, but never epilepsy. Menses were normal.

On examination the patient was small, not obese, with a round and plump face. The legs were obviously short,

especially proximally. Her nutrition was good (Fig. 6). Her height was 4 ft. 5 in., weight 78 lb., span 54 in., symphysis to soles 25 in. and symphysis to vertex 28 in. Chvostek's sign was positive and Trousseau's sign negative. The skin, hair and teeth were normal.

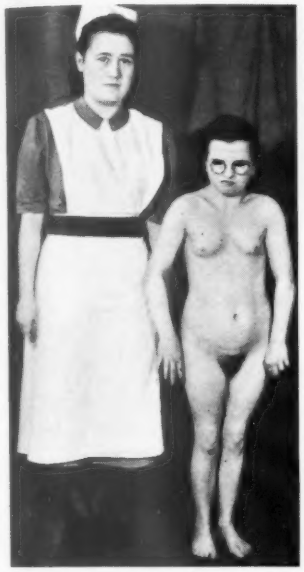

FIG. 6.—Case 2, V.C.E., with control of same age.

The patient wore thick glasses for myopia. Several streaks of opacity were seen in the crystalline lenses. Fundi were normal.

The finger nails were transversely ridged and bitten, but were probably within normal limits. The toenails were thickened and dystrophic. She had short, thick fingers and thumbs, especially the fourth and fifth fingers (Fig. 7).

The feet were normal.

No subcutaneous nodules were palpable. The blood pressure was 105/75 mm. Hg.

No other abnormalities were recorded.

INVESTIGATIONS. The serum calcium level was 8·0 mg. per 100 ml., serum phosphorus 5·8 mg. per 100 ml., and serum alkaline phosphatase 6·7 K-A units per 100 ml. No abnormalities were found in the urine. The Sulkowitch test was faintly positive. The output of 17-ketosteroids in 24-hour urine was 0·5 mg. per diem. This is well below the average for the patient's age. The radio-active iodine uptake was normal.

The serum sodium, potassium, urea and alkaline reserve were normal.

X-RAY EXAMINATION. The only bone abnormalities were in the hands. The fourth and fifth metacarpals were markedly shortened in both hands, and the first metacarpal also on the left (Fig. 8). Cranial bones, spine and bones of the extremities were otherwise normal. No obvious intracranial calcification was seen.

The chest was normal.

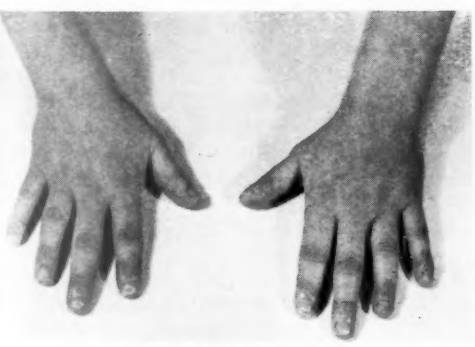

FIG. 7.—Hands of Case 2.

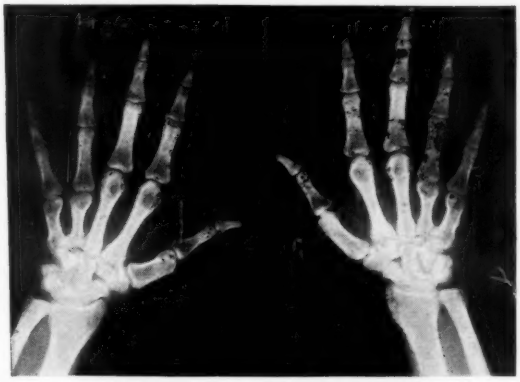

FIG. 8.—Case 2, radiograph of hands.

Widespread subcutaneous calcification, mostly of a finely mottled type, was seen in the hands, wrists, feet especially around the heels, and also in the suboccipital region, as well as at the back of the root of the neck.

MENTAL STATE. Her intelligence quotient was 68 and her mental age about 10.

ELLSWORTH-HOWARD TEST. See Fig. 2 and subsequent discussion.

RESPONSE TO PARATHYROID HORMONE. 'Parathormone' (Lilly) was injected intramuscularly for nine days in a dosage of 400 U.S.P. units daily, in two divided doses. She received therefore a total of 18 ml. (3,600 U.S.P. units) in the nine-day period. The serum calcium level before starting injections was 8·0 mg. per 100 ml., and serum phosphorus 5·8 mg. per 100 ml. The serum calcium at the end of the injections was 8·9 mg. per 100 ml., and serum phosphorus 5·0 mg. per 100 ml.

Case 3. T.F., aged 13 (date of birth April 13, 1940), an English boy, was delivered normally at home. He was breast fed with no difficulty. He sat up at 6 months, walked at 13 months, and cut his first teeth at 8 months. He started to have fits at 4½ years, which were controlled for a year with phenobarbitone, but then recurred more frequently in spite of treatment. He first went to school at 6 years old. He did not seem to learn, and after three years at school could neither read nor write. Because of backwardness he was tried at a special (for the educationally subnormal) school when aged 10, but fits demanded his return home, where he had been for a year before certification and admission to a mental deficiency hospital at the age of 12.

He had always been fat and a 'big eater'. Stiffness of the hands had been noticed at times for two years.

He had had measles, 'bronchial asthma' from about

6 months old, particularly before and after fits, and an electric burn of the hand when aged 5.

Two younger siblings were both healthy and of normal physique. The parents were well and unrelated. No family history of fits or nervous illness was given.

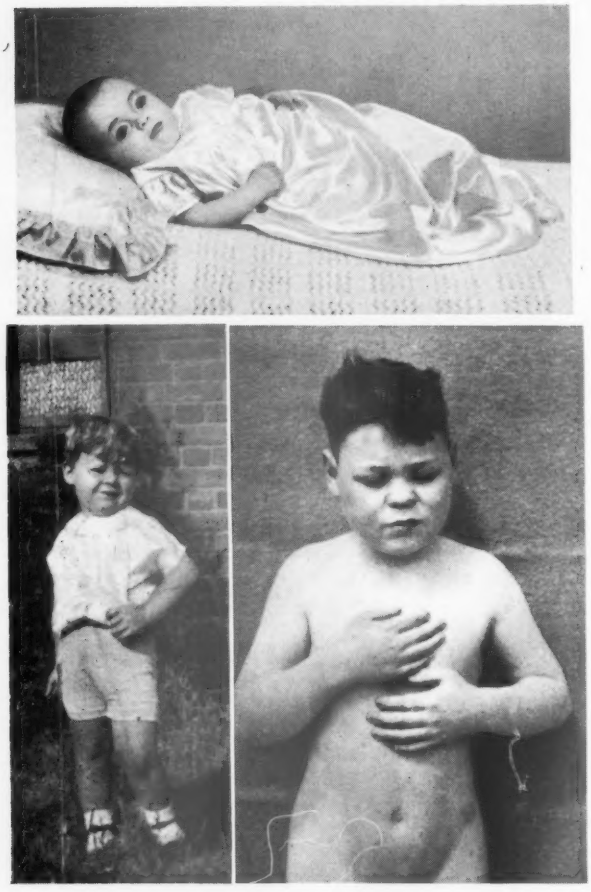

FIG. 9.—Case 3, T.F., aged 3 months, 5 years, and 14 years.

In the hospital for mental defectives he had major convulsions at approximately monthly intervals, in spite of regular phenobarbitone, 1 gr. daily. His mental age was 6. For six months he had been becoming very fat, gaining from 83 lb. in February, 1952, to 100 lb. in December, 1952. He was then put on thyroid, 1 gr. daily. In March, 1953, painful carpo-pedal spasms developed, and in the succeeding weeks he had several convulsions in rapid succession. Thyroid was discontinued and he was given calcium by mouth. As symptoms continued he was transferred to our unit for investigation.

On admission he was a fat, placid, friendly boy with a round face and a slow mind (Fig. 9). His weight was 95 lb., height 4 ft. 8 in., span 55 in., pubis to vertex 26½ in., and pubis to soles 29½ in. The Chvostek and Trousseau signs were positive.

All his teeth had erupted and appeared normal. The nails, skin and hair were normal.

The thumbs appeared short and did not extend more than half-way along the first phalanx of the index finger when outstretched.

Fine powdery opacities in the crystalline lenses were seen on slit lamp examination. The ocular fundi were normal.

His blood pressure was 150/120 mm. Hg in both arms.

No other abnormal physical signs were seen.

INVESTIGATIONS. The serum calcium level was 5·1 mg. per 100 ml., serum phosphorus 8·7 mg. per 100 ml., and serum alkaline phosphatase 25 K-A units per 100 ml. on admission.

On two occasions in May the urine showed a trace of albumin, but subsequently no albumin or other abnormality was detected. The urinary Sulkowitch reaction was negative. The total calcium in a 24-hour urine specimen was 25 mg. per 100 ml. The urinary 17-ketosteroid excretion was 4·9 mg. per diem, a normal result.

The serum sodium, potassium, chloride, urea and alkali reserves were normal. The total serum protein and albumin:globulin ratio were also normal.

The total fat excretion in faeces over a three-day period was 12 g.

RENAL FUNCTION TESTS. The Van Slyke urea clearance test, and the patient's power to concentrate and dilute his urine were both satisfactory.

ELECTROCARDIOGRAM. This was normal, except for prolongation of QTc to 0·47 sec.

CEREBROSPINAL FLUID EXAMINATION. Pressure was 120 mm. H_2O, cells fewer than 2 per c.mm., protein 60 mg. per 100 ml.

X-RAY EXAMINATION. Bone age and bone density were normal, without bone deformities. There was stippled symmetrical calcification in the basal ganglia, and very delicate calcification in the subcutaneous tissues on the inner aspect of both feet. A single spot was also seen on the radial side of the third metacarpal head but none elsewhere.

MENTAL TESTING. He was cooperative and a good test was possible. On the Terman-Merrill M (Revision) Scale his mental age was 6 years and 4 months (I.Q. 48). This compares with a test on the L Scales 18 months before, when his mental age was 6 years (I.Q. 51).

ELECTRO-ENCEPHALOGRAM. The resting record was dysrhythmic. Focal seizure activity (petit mal variant type) occurred in the right frontal lead, and was increased by overbreathing. The record was indicative of epilepsy.

Professor P. Cloake, of the Queen Elizabeth Hospital, Birmingham, compared this tracing with one taken by him three years before. He comments, 'The earlier tracing (1950) shows marked, diffuse abnormality, very suggestive of epilepsy. Your record shows less activity at 8 c/s than ours, but shows the 2-3 c/s activity upon which our report was largely based. Neither record

shows the marked fast activity and the dominant 6-7 c/s activity in the frontal areas which is said to be characteristic of hypoparathyroidism (Gotta and Odoriz, 1948).'

BLOOD-PRESSURE. On admission, and for two weeks afterwards, his blood-pressure was elevated, ranging from 130/110 to 160/130 mm. Hg. It then gradually fell to 130/80 mm. Hg, but remained subject to fluctuation throughout his hospital stay. There was a suggestion that his blood pressure would rise for a few days before and after a fit, but a rise and fall occurred sometimes independently of these, and seemed also independent of serum calcium variations and of clinical tetany or latent tetany. Although Albright states that hypertension is not an uncommon finding in pseudo-hypoparathyroidism (Albright *et al.*, 1952), study of published cases does not bear this out.

ELLSWORTH-HOWARD TEST. The patient's response to intravenous parathyroid hormone was tested on two occasions and the results are set out in Fig. 2, and discussed below.

PARATHYROID BIOPSY. On October 14, 1953, an exploratory operation on the neck was performed by Mr. G. C. Taylor. The right lateral lobe of the thyroid gland was freed and dislocated towards the mid-line, exposing the whole of its anterior and posterior surfaces. No evidence of parathyroid tissue was found during a careful and extensive dissection. Fragments of tissue removed and examined histologically consisted of thymus and thyroid tissue only.

PROGRESS IN HOSPITAL. For a few days after admission he was mentally confused and rather drowsy, and was subject to frequent generalized convulsions. Chvostek and Trousseau signs were very active, and carpo-pedal spasms occurred spontaneously on a few occasions. During this period it was observed that an intravenous injection of 10 ml. of a 10% calcium gluconate solution made no difference to his Chvostek reaction.

From the time that a small addition of calcium chloride was made to his diet, latent tetany varied in intensity, the Chvostek sign being negative during the greater part of the time. Convulsions also became less frequent and occurred about once monthly. No significant decrease in his fits was noted when he was given continuous phenobarbitone. His mind became quite clear, though slow, and he mixed happily with the other children, and took an intelligent interest in ward affairs. Coincidentally there was a rise in serum calcium from the initial low level of 5·1 mg. per 100 ml. to between 7 and 8 mg. per 100 ml., which level with fluctuations commented on below, was maintained through the greater part of his hospital stay.

TREATMENT. Table 1 illustrates the dietary additions and drugs that he received, and records beside them the fluctuations in his serum calcium and phosphorus levels. By the use of a low phosphorus diet, and again later by adding aluminium hydroxide to the diet (Albright, Burnett, Parson and Sulkowitch, 1941), it was hoped to increase the serum calcium by selectively favouring its absorption from the intestine (Shelling and Goodman, 1934; Anderson and Lyall, 1939). No such effect was observed in this case, although the effectiveness of the aluminium hydroxide regime in reducing phosphorus absorption was proved by a considerable sustained drop in urinary phosphorus excretion. Urinary phosphorus in mg. per hour was estimated daily on urine specimens collected between 6.0 p.m. and 6 a.m. approximately. For the period September 17 to October 2, during which he was on a normal diet, the averaged nightly output of phosphorus was 29·8 mg. per hour. From October 3 to November 9, while receiving aluminium hydroxide, this figure had dropped to 12·4 mg. per hour.

EFFECT OF PARATHYROID HORMONE. From September 2 to 10 he was given daily 100 U.S.P. units 'parathormone' (Lilly) by intramuscular injection, and from September 10 to 17 200 U.S.P. units daily. The variations of serum calcium and phosphorus in this period are shown graphically in Fig. 1. During the period September 3 to 17 the nightly urinary excretion of phosphorus averaged 30·2 mg. per hour, which will be seen to differ hardly at all from the period when he was on normal diet without additions. A rise in serum calcium and a drop in serum phosphorus which were co-extensive with the 'parathormone' dosage period were observed. Although fluctuations had previously been observed to occur spontaneously within even wider limits, the serum calcium had never previously changed consistently in the same direction for so long a time, and this result, coupled with an immediate fall when the hormone was stopped, offers presumptive evidence of an effect, albeit sluggish.

EFFECT OF DIHYDROTACHYSTEROL (A.T.10). This was given in gradually rising dosage for eight weeks. No effect at all was demonstrated on serum electrolytes, nor did the patient's urinary Sulkowitch reaction become more than transiently positive, in spite of the enormous final dosage of 50 mg. daily. A natural curiosity to discover how high a dosage he would tolerate had to be curbed by the expense of the drug, which in the final period was costing £3 a day. The manufacturers, Messrs. Bayer and Co., report that the batch of A.T.10 used had been checked and found to be biologically active. Absolute resistance to dihydrotachysterol does not seem to have been observed in other cases of pseudo-hypoparathyroidism, although tolerance to increased dosage has been commented upon by Albright *et al.* (1942), and some other authors. The majority of published cases seem to have reacted normally to the drug. Apparently resistance to A.T.10 is not confined to pseudo-hypoparathyroidism, for Blohm, Wurl, Gillespie and Escamilla (1953) describe inadequate response in a case of post-thyroidectomy tetany, while Moehlig and Steinbach (1954), found a similar case while simultaneously receiving cortisone to be totally unresponsive to A.T.10 and other drugs.

EFFECT OF CALCIFEROL. For the treatment of spontaneous hypoparathyroidism it is generally agreed that calciferol and A.T.10 are equally effective (McLean,

TABLE 1

DIET AND DRUG REGIMES IN CASE 3 (T.F.) WITH SERUM CALCIUM AND PHOSPHORUS LEVELS

Date	Regimes	Date	Ca (mg. per 100 ml.)	P (mg. per 100 ml.)
4-18. 5.53	Normal diet	5. 5.53	5·1	8·7
18. 5.53	Normal diet + 12 gr. Ca chloride daily (with accidental gap of one week from 25.5.53 to 3.6.53)	15. 5.53	5·8	7·8
		5. 6.53	7·8	6·9
		18. 6.53	8·4	9·4
8. 7.53	Low phosphorus diet + 12 gr. Ca chloride	16. 7.53	8·2	8·8
27. 7.53	Low phosphorus diet + 12 gr. Ca chloride + 6 drachms Aludrox daily	7. 8.53	8·1	8·2
10. 8.53	Low phosphorus diet + 12 gr. Ca chloride + 3 oz. Aludrox daily	19. 8.53	7·7	7·5
15. 8.53	Normal diet + 12 gr. Ca chloride + 3 oz. Aludrox daily	21. 8.53	10·3	5·3
21. 8.53	Normal diet + 12 gr. Ca chloride + 3 oz. Aludrox with meals daily	24. 8.53	8·8	4·4
31. 8.53	Normal diet, without additions	1. 9.53	6·9	8·0
2. 9.53	Normal diet + parathormone 100 units	8. 9.53	7·9	7·9
10. 9.53	Normal diet + parathormone 200 units	17. 9.53	9·0	6·5
17. 9.53	Normal diet, without additions	30. 9.53	8·2	7·6
2.10.53	Normal diet + 12 g. Ca lactate + 3 oz. Aludrox with meals daily	2.11.53	7·8	6·4
3.11.53	Normal diet + 6 g. Ca chloride + 3 oz. Aludrox with meals daily	7.11.53	8·1	6·7
23.11.53	Normal diet + 6 g. Ca chloride + thyroid 2 gr. + 3 oz. Aludrox with meals daily	1.12.53	7·8	7·7
3.12.53	Normal diet + A.T.10 3 mg. daily	8.12.53	7·6	7·8
15.12.53	Normal diet + A.T.10 5 mg. daily	15.12.53	8·1	7·7
17.12.53	Normal diet + A.T.10 7 mg. daily			
30.12.53	Normal diet + A.T.10 7 mg. + Ca lactate 4 g. daily	29.12.53	7·9	7·0
7. 1.54	Normal diet + A.T.10 30 mg. Ca lactate 4 g. daily	5. 1.54	7·5	8·4
		14. 1.54	7·0	8·6
21. 1.54	Normal diet + A.T.10 50 mg. + Ca lactate 4 g. daily	26. 1.54	7·9	8·4
28. 1.54	Normal diet + Calciferol 50,000 units + Ca lactate 4 g. daily	4. 2.54	8·2	7·2
5. 2.54	Normal diet + Calciferol 250,000 units + Ca lactate 4 g. daily	11. 2.54	7·3	7·4
12. 2.54	Normal diet + Calciferol 1,200,000 units + Ca lactate 4 g. daily	18. 2.54	8·9	6·7
		23. 2.54	10·3	6·8
25. 2.54	Normal diet + Calciferol 250,000 units + Ca lactate 4 g. daily	2. 3.54	10·9	7·7

1941); the former is usually preferred because it is less expensive. Calciferol seems to be also successful in the treatment of pseudo-hypoparathyroidism. This patient is no exception, though large doses were necessary to raise his serum calcium to a normal level (Table 1), and his serum phosphorus was relatively less affected.

EXPERIENCE WITH THE ELLSWORTH-HOWARD TEST. Hourly collections of urines, as suggested by Ellsworth and Howard in their original description of the test, are often difficult with patients of low intelligence. We have had to modify the test to two-hourly collections, and in one case three-hourly collections of urine, before and after giving 200 U.S.P. units 'parathormone' (Lilly) intravenously. For six hours before the injection and throughout the test only water was given by mouth. The results of the test on each of the cases of pseudo-hypoparathyroidism are shown in Fig. 2. Two tests were performed on Case 3. It will be seen that of the four tests, two showed some increase in urinary phosphorus, one a definite decrease and another showed a very slight increase. There was a decrease in urinary phosphorus in the case of steatorrhoea with tetany following intravenous 'parathormone'.

Fig. 2 also records our inability to show any immediate urinary phosphorus response to 'parathormone' injections in normal subjects, although in one normal subject there was an increase between the third and sixth hours after injection. Our experience is similar to that of Milne (1951) and Dent (1953). The results indicate that the Ellsworth-Howard test is of no value in differentiating between the 'normal response' and the so-called

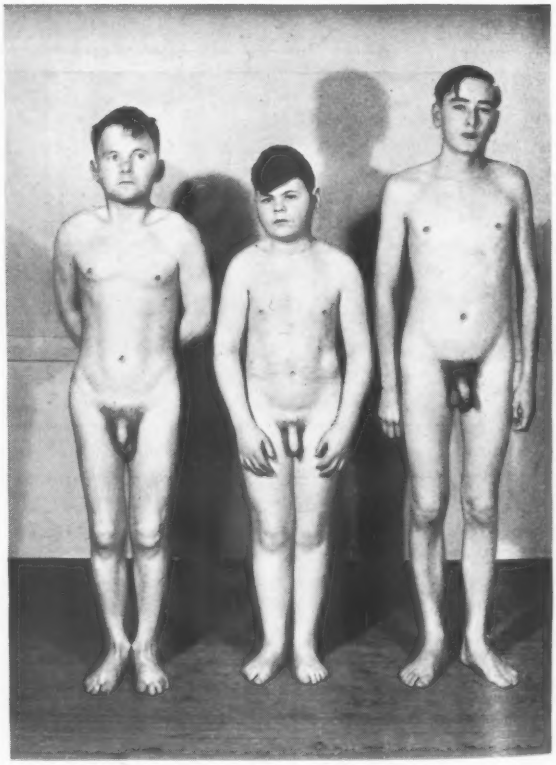

FIG. 8.—Cases 1 and 2, with a normal 15-year-old boy.

'resistant response' of pseudo-hypoparathyroidism. We have not had the opportunity to test the hormone preparation on cases of spontaneous hypoparathyroidism. Milne (1951) found in such cases a two- to three-fold increase in urinary phosphorus and Dent (1953) reported similar results in two cases of surgical hypoparathyroidism and no response in a third. In such cases Albright has found a tenfold increase.

It appears therefore to be established that the urinary-phosphorus-raising power of the 'parathormone' available in Britain is very much less than that present in the hormone preparation which Albright used. The manufacturers (Eli Lilly Co.) inform us, however, that the product available in Britain is the same as that sold in America.

Analysis of Foregoing 27 Cases of Chronic Tetany with Bone Changes or Ectopic Calcification

Age and Sex Incidence. In this group of 27 cases, 15 are female and 12 male. The youngest in the series is 7 years (Payne, 1953), and the oldest 49 years (Alexander and Tucker, 1949).

Race. Nine are American (one a Negro), four English, three Danish, three German, one Welsh, one Swiss, one Swedish, one French, one Italian and one a Russian Jew.

Presenting Symptom. In five tetany, or symptoms referable to muscular hyper-excitability (laryngospasm, wheezing, stridor), were first noticed. In 11 convulsions or 'attacks' brought the patient to medical notice. Two had no symptoms at all. Calcified skin lesions were the first symptoms in two, and two others presented with backwardness. 'Poor nerves' and 'excessive sleepiness' were the first symptoms of another two. In two cases there is no record on this point.

General Symptomatology. It is interesting that in spite of the presumably congenital nature of the malady, symptoms referable to hypocalcaemia were not experienced under the age of 2, and in most cases frank tetany was not apparent until the middle years of childhood or later, if indeed it was ever manifested. Convulsions, which occurred at some time in 16 cases, generally began in childhood and frequently before any sign of tetany had been noticed. Where the condition was recognized in infancy it was the development of calcific nodules in the skin that enabled this. Backwardness is almost the rule among them, and is reported in 19 of the 20 whose mentality is commented upon. One case (Alexander and Tucker, 1949) is reported to have had normal intelligence. The retardation does not seem to be very gross, though several have found their way into hospitals for the mentally defective. The lowest reported intelligence quotient was 50 (our Case 1). Many authors comment on the friendly, docile personalities of these patients, so-called 'smiling imbeciles'. Other factors besides basic personality may contribute to this slowness and passivity. In the first place a number of cases have been suspected of hypothyroidism. Himsworth and Maizels' (1940) case had a basal metabolic rate of 25% and was treated as a cretin. Lachmann's (1941) Case 59 was said to have a myxoedematous appearance, with a basal metabolic rate of −16%. Peterman and Garvey's (1949) case was diagnosed as hypothyroidism originally. Our Case 3 showed an unexpectedly low uptake of radio-active iodine, suggesting thyroid dysfunction, whereas Case 2, like that of Azerad *et al.* (1953), showed a normal uptake. It does not appear that the co-existing thyroid deficiency is a regular feature of the syndrome, though possibly present in some cases.

Secondly, several of the older patients showed signs of Parkinsonism, such as an immobile face, a lack of associated movements and a propulsive gait. One also had tremor. This feature is undoubtedly connected with the calcification of the basal ganglia that is visible in radiographs of these patients, and has also been seen in spontaneous hypoparathyroidism (Eaton and Haines, 1939). In four of this series these symptoms were commented upon (Alexander and Tucker, 1949; Gsell, 1950; Reynolds *et al.*, 1952; and in our Case 1).

Concerning sexual functions, several have shown delay in acquiring secondary sex characters. In three women menstruation started respectively at 17, 18 and 22 years of age. In one of these the periods were scanty and irregular, and in a fourth case also irregular menses were noted. One male had a delayed puberty (aged 22 years), and another aged 2½ had undescended testicles. Alexander and Tucker's (1949) patient, on the other hand, was married and had two normal children, while the presence of a strong sexual instinct may be deduced from the behaviour of our Case 1, who at the age of 21 years sexually assaulted a child of 4 years. It is noteworthy that Greene and Swanson (1941) describe eroticism as a feature of the mental disturbance of some cases of hypoparathyroidism. A reduced 17-ketosteroid output was observed in one of our cases, but normal values have been obtained in others.

Physique. A round face was specifically mentioned in 16 cases. Twenty out of 24 in whom height is recorded were dwarfed, that is to say were of less than the minimum height recorded for their ages in standard tables, or were less than 5 ft. in

height if adult. Four were within normal limits for height, but these were aged $3\frac{1}{4}$, $2\frac{1}{2}$, $9\frac{1}{4}$ and 13 years when they were measured, and may have shown retardation of growth later. One other is described as 'stocky', but measurements are not given. Dwarfism was disproportionate in five cases, the limbs being preponderantly shortened. Twelve cases were described as obese; none were thin or underweight. Nine of them were recorded as having been fat from infancy, and at least two reached extraordinary weights when babies. Thus, Alexander and Tucker's (1949) case weighed 45 lb. when 9 months old, while Scott and Temple's (1949) case is said to have weighed 32 lb. at 5 months, and 67 lb. at 14 months! It is perhaps worth recording that three of this group of 27 cases are said to have had red hair.

Skeletal Changes. The alterations in the radiological outlines of certain bones that Albright and his colleagues observed have already been recounted. In reviewing the 27 cases that we have collected, we have tabulated skeletal changes as follows:

Total number showing bone changes	20
Metacarpal changes	20
Metatarsal changes	6
Phalangeal changes	7
Exostoses	3
Bowing of bones	4
Early closure of epiphyses	5
Generalized osteoporosis	6
Generalized osteosclerosis	2

Metacarpal and metatarsal changes follow exactly the pattern outlined by Albright, and the second and third bones were seldom involved. Changes in metatarsals or phalanges were never present unless there were changes in the metacarpals too. Whereas changes in bone density are seldom encountered in spontaneous hypoparathyroidism, variations in both directions are recorded in this group, and osteoporosis was striking in the case of Reynolds *et al.* (1952) and in our Case 1.

Elrick *et al.* (1950) drew attention to another disease state in which brachydactyly is conjoined with ectopic calcification, namely progressive myositis ossificans. We may refer to two other abnormalities which in their osseous manifestations bear an even closer resemblance to pseudo-hypoparathyroidism. These are familial brachydactyly (Brailsford, 1945), and chondroectodermal dysplasia (Ellis and van Creveld, 1940). In the former condition there are metacarpal and metatarsal changes identical with those we are studying, and sometimes these are accompanied by exostosis formation. In chondro-ectodermal dysplasia, the bone disorder, in spite of many resemblances to pseudo-hypoparathyroidism, shows some distinctive features, but the clinical likeness is made closer by coexisting changes in teeth, nails and hair, and occasionally also by localized soft tissue calcification in the former condition.

Bone dystrophy was absent in seven patients in this series, all of whom of course showed subcutaneous calcification. In another eight bone changes were present without a report of calcification in the tissues, though it was not always specifically looked for.

Subcutaneous Calcification. This was observed in 19 patients, 12 of whom had bone changes as well. Most often it took the form of scattered small fragments in the limbs, especially in the hands and feet; larger palpable nodules and plaques were found in some cases, in any situation. In several biopsy demonstrated actual bone formation in these. How early these lumps appeared in two cases has already been mentioned. They are usually painless, though some tenderness was present over a large plaque in the upper part of the cheek of our Case 1.

Other Findings. Cataracts were noticed in 12 patients, and symmetrical calcification of the basal ganglia (Eaton and Haines, 1939) in ten. Although Reynolds *et al.* (1952) commented that the incidence of intracranial calcification seemed unusually high in pseudo-hypoparathyroidism (and this might be expected if it is looked upon as a secondary change, and the disease is congenital), nevertheless this figure represents but a third of the total. In truth, the numbers are probably greater, for several are not recorded to have had radiographs of the skull taken.

Ectodermal defect was commonest in the teeth, but in contrast to reports of spontaneous hypoparathyroidism, changes in hair or nails are seldom commented upon. Two of this series developed exfoliative dermatitis, and one died as a result.

Serum calcium and phosphorus levels were generally within the usual range for hypoparathyroidism (calcium 4 to 8 mg. per 100 ml., phosphorus 4 to 13 mg. per 100 ml.), though a serum calcium reading of 10·8 mg. per 100 ml. on Selye's (1949) Case 2 should be noted. Three cases, all children, had slightly elevated serum alkaline phosphatase levels (15 Bodansky units, 24 and 25 King-Armstrong units per 100 ml. respectively).

In these 27 cases parathyroid hormone, whenever tried, elicited no more than a very slight increase in serum calcium, in whatever dosage it was used. We believe that the conjunction of chronic tetany with these specific radiological findings will allow a patient to be labelled as pseudo-hypopara-

thyroidism, and by this diagnosis it is implied that the serum calcium response to parathyroid hormone will prove to be greatly reduced or absent, in striking contrast with the responses obtained in surgical or spontaneous hypoparathyroidism.

To this nucleus of pseudo-hypoparathyroidism, two other cases from the literature can be added on the strength of a clearly demonstrated deficiency in response to parathyroid hormone after a trial in satisfactory dosage, even though in these cases metacarpal changes and calcifications are wanting. Brief summaries of these two cases (Albright *et al.*, 1942, Case 2; and Elrick *et al.*, 1950, Case 1) now follow.

Albright *et al.* (1942), Case 2. American girl aged 12 years, always overweight and mentally dull. Tetany from 3 years of age. Positive Chvostek reaction. Serum calcium 8·9 mg. per 100 ml., phosphorus 6·3 mg. per 100 ml. Increased radiological density of bones. Negative Ellsworth-Howard test. Several injections of 500 U.S.P. units of parathyroid hormone had no effect on serum levels of calcium and phosphorus. Response to A.T.10 in dosage of 10 to 15 mg. daily.

Elrick *et al.* (1950), Case 1. American man aged 27 years. Fits for 15 years, tetany for one year. Round faced, short (height 4 ft. 10 in.). Mentally retarded (I.Q. 69). Latent tetany, cataracts, calcification of basal ganglia; no teeth. Ellsworth-Howard test negative. Serum calcium 7·0 per 100 ml., phosphorus 12 mg. per 100 ml. No response to five days of parathyroid hormone in a dosage of 500 U.S.P. units daily, but ready response to A.T.10. Parathyroid biopsy showed hyperplasia of gland.

In our opinion the foregoing account incorporates the only cases of pseudo-hypoparathyroidism in the literature which can be accepted unequivocally on the published evidence. They number 25, and they are briefly summarized in the appendix, where some details of an unpublished child with the same condition are also to be found.

Two cases reported under this label by Albright and his colleagues have been rejected.

Elrick *et al.* (1950), Case 3. American woman aged 34 years. She, and an identical twin sister, had had tetany all their lives, especially at the menses. In both hypertension had developed at 33 years of age. Height 4 ft. 3 in., round face. Latent tetany, calcification of basal ganglia. Blood pressure 190/115 mm. Hg. Ellsworth-Howard test 'decreased sensitivity to parathyroid hormone'. Parathyroid biopsy showed hyperplasia of the gland.

This case rests for diagnosis on physique and response to the Ellsworth-Howard test, neither of which can be regarded as conclusive. The positive family history is further evidence for pseudo-hypoparathyroidism but again is not decisive (see above). At present the biopsy finding, though of great interest, is not of much evidential value.

Elrick *et al.* (1950), Case 4. American girl aged 9 years. Tetany since 4 years, and asthma. Height 4 ft. 8 in. Latent tetany. Ellsworth-Howard test 'decreased sensitivity'.

As published, this case relies for diagnosis on the Ellsworth-Howard test, and so cannot be accepted.

In the literature there are a number of other cases which offer some grounds for thinking that they may be cases of pseudo-hypoparathyroidism, though proof is wanting. These have been reported under various labels, and brief summaries are appended below.

Kirklin and Childrey (1936). American girl of 19 years. Tetany from 12 years of age. Dull mentality, Cataracts. Short, stubby fingers. Serum calcium 5·2 mg. per 100 ml., phosphorus 8·5 mg. per 100 ml. Hypothyroid appearance. Basal metabolic rate 15%.

Reported as 'spontaneous parathyroid tetany'.

Martin and Bourdillon (1940). Italian male of 39 years. Tetany since 5 years old. 'Mediocre' intellectual development; worked as a tailor. Short, bald. Latent tetany. Dense bones in radiographs. Serum calcium 6·7 mg. per 100 ml., phosphorus 4·8 mg. per 100 ml. No clinical response to several injections of 100 U.S.P. units parathyroid hormone.

Reported as 'chronic idiopathic tetany'.

Lachmann (1941), Case No. 71. Danish woman aged 37 years. Winter tetany since 15 years old. Cataracts, psoriasis. Delicately built with short extremities, height 4 ft. 5 in. Mental development below average. Very small breasts and scanty pubic hair. Diffuse thyroid enlargement. Treated with parathyroid hormone and calcium but no effect on symptoms or serum calcium. Serum calcium 6·8 mg. per 100 ml. A brief trial of small doses of A.T.10 had no effect.

Case presented as 'idiopathic hypoparathyroidism'. Details of parathyroid dosage wanting.

Moehlig and Gerische (1950). Armenian male of 19 years. Fits since 12 years of age. Thickset, heavy (121 lb.) and round faced, height 4 ft. 9 in., with short extremities. Latent tetany. Short hands. Unerupted and dystrophic teeth. Coarse trabeculation of certain bones in radiographs. Serum calcium 4·7 mg. per 100 ml. No response to Ellsworth-Howard test. Reacted well to A.T.10.

This case was reported as 'pseudo-hypoparathyroidism' but depends on the Ellsworth-Howard test for diagnosis.

Jordan and Kelsall (1951). English boy of 16 years. Onset of tetany aged 9 years. Convulsions. Mentally alert; short and sturdy. Height 4 ft. 9 in. Dystrophic teeth. Cataracts. Sclerosis of bones. Intracranial

calcification. Serum calcium 6·3 mg. per 100 ml., phosphorus 9·1 mg. per 100 ml. Very sluggish response of serum calcium and urinary phosphorus excretion after 200 U.S.P. units parathyroid hormone.

Reported as 'idiopathic hypoparathyroidism'.

Berardinelli (1951). Brazilian girl of European ancestry, aged 16 years. Epilepsy and diabetes insipidus from age 4 years. Height 4 ft. 8 in. Obese, anxious, highly intelligent. Latent tetany. Intracranial calcification. Serum values of calcium and phosphorus not obtained. Treated with 100 U.S.P. units parathyroid hormone daily for 40 days without clinical response. Response to A.T.10 was immediate (abolition of anxiety and positive Sulkowitch reaction in urine).

Presented as 'pseudo-hypoparathyroidism and diabetes insipidus'. Besides the latter disorder, the high intelligence and lack of serum electrolyte values make the diagnosis difficult to substantiate.

Wise and Hart (1952), Case 3. Puerto Rican woman aged 24 years. Convulsions from age 1 year. Mentally backward, I.Q. 57. Dwarfed but well proportioned. Height 4 ft. 2 in. Dystrophic teeth. Cataracts. Cerebral calcification. Serum calcium 3·8 mg. per 100 ml., phosphorus 10 mg. per 100 ml. Gave birth to an unaffected infant after a normal pregnancy, aged 24 years. Ellsworth-Howard test negative. Brisk response to A.T.10.

The authors suggest that this is a case of pseudo-hypoparathyroidism but do not regard this as proved without a biopsy of a parathyroid gland.

One further case was reported as pseudo-hypoparathyroidism by Lowe *et al.* (1950). There are a number of anomalous features in this patient, an American boy of 4 years whose symptoms date from early infancy, and in whom tetany was associated with prolonged steatorrhoea. The child's physique and mentality were not those of other cases of pseudo-hypoparathyroidism, and the case is best regarded as one of steatorrhoea with tetany. Some x-ray changes in the metacarpals were noted, but these are uncharacteristic, and the diagnosis rests very insecurely on the results of the Ellsworth-Howard test.

Incidence of the Disease

It should now be clear that the symptomatology of these cases is very varied. They may come to notice in childhood or later with epilepsy, with mental backwardness, with dwarfism, with obesity, with cataracts or with skin lesions, and with or without tetany. Although only one case has so far been published as pseudo-hypoparathyroidism in the British literature (Bishop and de Mowbray, 1951), reasons have already been given for thinking that the cases of Himsworth and Maizels (1940) and of Richardson (1946) are also examples.

We discovered accidentally one of our cases (Case 3) in a mental deficiency institution, and so it seemed advisable to seek for other cases hidden in such hospitals. A postal enquiry to some 100 mental deficiency hospitals in Great Britain subsequently brought two other cases (our Cases 1 and 2) to light. Both Lachmann (1941) and Bakwin *et al.* (1950) suggest that collections of mental defectives probably include unrecognized cases of hypoparathyroidism, and the latter authors examined the hands of 1,000 epileptics in a colony for evidence of pseudo-hypoparathyroid deformity, with negative results.

We searched for other cases of hypoparathyroidism by serum calcium or phosphorus estimations on a group of unselected epileptic children attending hospital as out-patients, on a group of children with cataracts in a school for the partially sighted, and on a group of 150 mentally defective epileptic children in an institution. No further examples were found.

The literature concerning osteoma of the skin, reviewed by Vero, Machacek and Bartlett (1945), does not appear to contain other recognizable cases of this disease.

Some idea of the rarity of pseudo-hypoparathyroidism may be derived from Wise and Hart's (1952) figures. In a large hospital in the United States with 62,000 admissions yearly only one possible case was detected in a 10-year survey. However it may be that some cases do not reach general hospitals at all.

Discussion

What is the reason for the discrepancy between the results obtained by Albright and other American workers concerning the effect of parathyroid hormone on the excretion of urinary phosphorus, and those of Dent (1953), Milne (1951) and ourselves?

Commercial parathyroid extract is assayed biologically on its power to raise the serum calcium level of dogs. This method of assay would be satisfactory if the physiological action of the hormone was that envisaged by Dent (1953), namely that it increases calcium and phosphorus in the serum by its stimulating action on osteoclasts. This would result in a raised calcium:phosphorus product, which returns to normal via enhanced phosphorus excretion. Accordingly, the increase in urinary phosphorus is dependent upon the raised serum calcium level. On the other hand, were Albright's hypothesis of parathyroid action the right one, namely that the hormone directly stimulates the kidney to excrete phosphate, and that the rise in serum calcium is secondary to a consequent fall

in serum phosphorus level, then this would imply that the many batches of 'parathormone' recently used in Britain were of very low potency or even inactive.

There is, however, ample evidence that the hormone as received in Britain has serum calcium-raising power. Dent (1953) showed that although he could not produce hyperphosphaturia in normal subjects they did display a slight but definite rise in serum calcium, and this has also been our experience. Moreover our patient 3 showed a rise in serum calcium whilst being given high doses of the drug over a long period. In cases of spontaneous or post-operative hypoparathyroidism appearing in the British literature the extract has been shown to be completely satisfactory in serum calcium-raising power (Dent, 1953).

The only satisfactory explanation of these results is to be found in recent work on parathyroid extracts. This has provided evidence that there are two active hormones present in the extracts. L'Heureux, Tepperman and Wilhelmi (1947) have identified two proteins in parathyroid extract by electrophoresis in the Tiselius apparatus. Stewart and Bowen (1952) have reported that preparations of parathyroid hormone after treatment with formaldehyde lose their power to raise the serum calcium level of dogs whilst still being able to increase the excretion of urinary phosphorus. Davies and Gordon (1953) have been successful in isolating and separating two hormones from parathyroid glands, one being responsible for calcium-raising power and the other hormone increasing urinary phosphorus.

The explanation of the difference in the response to parathormone found by Albright and the response found by more recent British investigations, therefore, may be that over a period of years changes have been made in the processes of manufacture of the extract, which have not affected its serum calcium-raising power but have altered its power to increase urinary phosphorus.

The difference of response between normal and pseudo-hypoparathyroid subjects is one of the bases of Albright's 'target-organ defect' hypothesis. This difference we have been unable to confirm. Furthermore, if the parathyroid gland excretes two hormones, and we feel there is very strong evidence for this, then there would have to be two simultaneous 'target-organ defects' in pseudo-hypoparathyroidism.

Again, the defect, if it exists, must be incomplete at one end-organ, because parathyroid extract is sometimes able to provoke a rise in serum calcium in pseudo-hypoparathyroidism. For the above reasons it seems likely to us that some other explanation than end-organ insensitivity is at the root of the puzzling responses of these cases, and particularly because we have encountered precisely similar aberrations in response in some cases of steatorrhoea with tetany.

Summary

The clinical features of pseudo-hypoparathyroidism, first defined and named by Albright and his colleagues, are described, examined, and contrasted with those of spontaneous hypoparathyroidism.

Using only the diagnostic criteria that are considered to be valid, 25 published accounts of pseudo-hypoparathyroidism have been collected.

Three new case reports are added to these, and some details are provided of another unpublished case. A group of 27 cases is then surveyed, and some other unproven cases possibly of the same type are described.

Certain difficulties were encountered in trying to reproduce the responses to parathyroid hormone that other workers have obtained in normal and pseudo-hypoparathyroid subjects, and the bearing of these upon the nature of the disorder is debated.

Our thanks are due to the following people who have helped us: To Dr. J. V. Morris for permission to study Case 1, to Dr. T. B. Jones for permission to study Case 2, to Dr. J. C. Rohan for referring Case 3 to our care and for carrying out mental tests on him, to Drs. W. W. Payne and A. I. Cheyne for details of cases discussed in the text, to Dr. M. Israelski for x-ray reports, to Dr. C. Tetlow for electroencephalogram reports, to Dr. S. F. Whittaker for assistance in finding hospital beds for our cases, to Dr. John Sheward for the photograph of Case 3, to Mr. H. Quinton for performing tests of thyroid function on Cases 2 and 3, and to Miss L. O. Morris for help with biochemical estimations.

References

Alexander, S. and Tucker, H. (1949). *J. clin. Endocr.*, **9**, 862.
Albright, F., Burnett, C., Parson, W. and Sulkowitch, H. (1941. *J. clin. Invest.*, **20**, 445.
——, ——, Smith, P. and Parson, W. (1942). *Endocrinology*, **30**, 922.
—— and Ellsworth, R. (1929). *J. clin. Invest.*, **7**, 183.
——, Forbes, A. and Henneman, P. (1952). *Trans. Ass. Amer. Phys.*, **65**, 337.
—— and Reifenstein, E. (1948). *The Parathyroid Glands and Metabolic Bone Disease*. Baltimore.
Anderson, I. and Lyall, A. (1939). *Quart. J. Med.*, **8**, 209.
Aub, J. (1935). *J. Amer. med. Ass.*, **105**, 197.
Azerad, E., Gatha, J. and Raverdy, P. (1953). *Bull. Soc. Méd. Hôp. Paris*, **69**, 199.
Bakwin, H., Gorman, W. and Ziegra, S. (1950). *J. Pediat.*, **36**, 567.
Barr, D., MacBryde, C. and Sanders, T. (1938). *Trans. Ass. Amer. Phys.*, **53**, 227.
Berezin, S. and Stein, J. (1948). *J. Pediat.*, **33**, 346.
Berardinelli, W. (1951). *Acta endocr., Kbh.*, **7**, 7.
Bille, B. (1952). *Acta paediat., Uppsala*, **41**, 380.
Bishop, P. and Mowbray, R. de (1951). *Proc. roy. Soc. Med.*, **44**, 952.
Blohm, R., Wurl, O., Gillespie, J. and Escamilla, R. (1953). *J. clin. Endocr.*, **13**, 519.
Brailsford, J. (1945). *Brit. J. Radiol.*, **18**, 167.
Brimblecombe, F. (1949). *Archives of Disease in Childhood*, **24**, 77.
Camp, J. (1947). *Radiology*, **49**, 568.
Cantarow, A. (1932). *Arch. Pediat.*, **49**, 293.
——, Stewart, H. and Morgan, D. (1939). *Endocrinology*, **24**, 556
Cantor, M. and Scott, J. (1942). *Canad. Ass. med. J.*, **47**, 551.

Davies, B. and Gordon, A. (1953). *Nature, Lond.*, **171**, 1122.
Dent, C. (1953). *Proc. roy. Soc. Med.*, **46**, 291.
Drake, T., Albright, F., Bauer, W. and Castleman, B. (1939). *Ann. intern. Med.*, **12**, 1751.
Eaton, L., Camp, J. and Love, J. (1939). *Arch. Neurol. Psychiat., Chicago*, **41**, 921.
—— and Haines, S. (1939). *J. Amer. med. Ass.*, **113**, 749.
Ellis, R. and Creveld, S. van (1940). *Archives of Disease in Childhood*, **15**, 65.
Ellsworth, R. and Howard, J. (1934). *Bull. Johns Hopk. Hosp.*, **55**, 296.
Elrick, H., Albright, F., Bartter, F., Forbes, A. and Reeves, J. (1950). *Acta Endocr., Kbh.*, **5**, 199.
Emerson, K., Walsh, F. and Howard, J. (1941). *Ann. intern. Med.*, **14**, 1256.
Franco, S. (1940). *Ibid.*, **14**, 529.
Gillam, G. and Morton, F. (1953). Personal communication.
Goerner, A. and Samuelsen, G. (1934). *J. Amer. med. Ass.*, **102**, 1001.
Gotta, H. and Odoriz, J. (1948). *J. clin. Endocr.*, **8**, 674.
Grant, D. (1953). *Quart. J. Med.*, **22**, 243.
Greene, J. and Swanson, L. (1941). *Ann. intern. Med.*, **14**, 1233.
Gsell, O. (1950). *Dtsch. med. Wschr.*, **75**, 1117.
Himsworth, H. and Maizels, M. (1940). *Lancet*, **1**, 959.
Humphreys, H. (1939). *Proc. roy. Soc. Med.*, **32**, 633.
Hunter, D. (1931). *Quart. J. Med.*, **24**, 393.
Jordan, A. and Kelsall, A. (1951). *Arch. intern. Med.*, **87**, 242.
Kirklin, O. and Childrey, E. (1936). *Proc. Mayo Clin.*, **11**, 15.
Lachmann, A. (1941). *Acta med. scand.*, Suppl. 121.
L'Heureux, M., Tepperman, H. and Wilhelmi, A. (1947). *J. biol. Chem.*, **168**, 167.
Leonard, M. (1946). *J. clin. Endocr.*, **6**, 493.
Leopold, S. and Jonas, L. (1932). *Amer. J. med. Sci.*, **183**, 418.
Levy, H. (1947). *Med. Clin. N. Amer.*, **31**, 243.
Liu, S. (1928). *J. clin. Invest.*, **5**, 277.
Lowe, C., Ellinger, A., Wright, W. and Stauffer, H. (1950). *J. Pediat*, **36**, 1.
MacBryde, C. (1938). *J. Amer. med. Ass.*, **111**, 304.
Martin, E. (1953). *Wien. Z. inn. Med.*, **34**, 177.
—— and Bourdillon, J. (1940). *Rev. méd. Suisse rom.*, **60**, 1166.
——, Guye, P., Babel, J. and Courvoisier, B. (1952). *Ann. Endocr., Paris*, **13**, 943.
McLean, F. (1941). *J. Amer. med. Ass.*, **117**, 609.
McQuarrie, I., Hansen, A. and Ziegler, M. (1941). *J. clin. Endocr.*, **1**, 789.
Medill, E. (1951). *Brit. J. Radiol.*, **24**, 685.
Milne, M. (1951). *Clin. Sci.*, **10**, 471.
Moehlig, R. and Gerische, R. (1950). *J. clin. Endocr.*, **10**, 1609.
—— and Steinbach, A. (1954). *J. Amer. med. Ass.*, **154**, 42.
Morgan, J. (1936). *Arch. Path., Chicago*, **21**, 10.
Morgan, T. (1915). *Proc. Soc. exp. Biol., N.Y.*, **13**, 31.
Mortell, E. (1946). *J. clin. Endocr.*, **6**, 266.
Payne, W. (1953). Personal Communication.
Peterman, M. and Garvey, J. (1949). *Pediatrics*, **4**, 790.
Pope, A. and Aub, J. (1944). *New Engl. J. Med.*, **230**, 698.
Reifenstein, E. (1950). In *Textbook of Endocrinology*, ed. Williams, R. H. Philadelphia.
Reynolds, T., Jacobson, G., Edmondson, H., Martin, H. and Nelson, C. (1952). *J. clin. Endocr.*, **12**, 560.
Richardson, J. (1946). *Proc. roy. Soc. Med.*, **39**, 514.
Salvesen, H. (1930). *Acta med. scand.*, **73**, 511.
Schüpbach, A. and Courvoisier, B. (1949). *Schweiz. med. Wschr.*, **79**, 887.
Scott, E. and Temple, W. (1949). *Amer. J. Dis. Child.*, **77**, 758.
Selye, H. (1949). *Textbook of Endocrinology*, 2nd ed. Montreal.
Shelling, D. and Goodman, M. (1934). *J. Amer. med. Ass.*, **102**, 669.
Siglin, I., Eaton, L., Camp, J. and Haines, S. (1947). *J. clin. Endocr.*, **7**, 433.
Simpson, J. (1952). *Brain*, **75**, 76.
—— (1954). *Brit. J. Derm. Syph.*, **66**, 1.
Simpson, K. (1953). *Gt Ormond St. J.*, **3** (no. 5), 54.
Sprague, R., Haines, S. and Power, M. (1945). *J. Lab. clin. Med.*, **30**, 363.
Stewart, G. and Bowen, H. (1952). *Endocrinology*, **51**, 80.
Sugar, O. (1953). *Arch. Neurol. Psychiat., Chicago*, **70**, 86.
Sutphin, A., Albright, F. and McCune, D. (1943). *J. clin. Endocr.*, **3**, 625.
Thorpe, E. and Handley, H. (1929). *Amer. J. Dis. Child.*, **38**, 328.
Uhlemann, H. (1950). *Klin. Wschr.*, **28**, 489.
Vero, F., Machacek, G. and Bartlett, F. (1945). *J. Amer. med. Ass.*, **129**, 728.
Wise, B. and Hart, J. (1952). *Arch. Neurol. Psychiat., Chicago*, **68**, 78.

APPENDIX

Summaries of 23 Cases of Hypoparathyroidism Reported in the Literature Exhibiting Bone Changes, Subcutaneous Calcification or Both

1. Himsworth and Maizels (1940). English boy of 14 years. Onset of fits aged 5 years. Growth and mentality retarded. Sturdy build. Height 4 ft. 5 in., weight 81 lb. Red hair. Appeared hypothyroid. Basal metabolic rate 25%. Latent tetany. Cataracts. Bone density normal. Calcified nodules around knee joints. Serum calcium 5 mg. per 100 ml. No effect from two weeks of parathyroid extract, but response to A.T.10 and Vitamins D2 and D3.

Reported as 'congenital thyroid and parathyroid deficiency'.

2. Lachmann (1941), Case 57. Danish woman of 48. One of five children, two siblings being Cases 58 and 59 *infra*. The eldest sister had a cataract operated on at 36 years, was said to be 'queer' mentally, had a haemorrhage of the brain at 50, and died at 53. The youngest sibling, a boy, was normal.

This patient was well throughout her life and had no symptoms. Small and well proportioned. Height 4 ft. 5 in., weight 113 lb. Thumbs and fourth toes very short. Partial syndactyly toes 2 and 3. In radiograph, symmetrical under-development of fourth metatarsals. Serum calcium 8·7 mg. per 100 ml., phosphorus 4·8 mg. per 100 ml.

3. Lachmann (1941), Case 58. Danish woman aged 39. Sister of cases 57 and 59. 'Poor nerves' always. Scanty, irregular menses. Psoriasis for three years. Small, delicate frame. Height 4 ft. 3 in., weight 111 lb. Cretinoid appearance. Basal metabolic rate 16%. Intelligence below average. Cataracts. Bones of fifth finger very short, and styloid process of ulna detached in radiographs. Died with exfoliative dermatitis. Serum calcium 8·1 mg. per 100 ml. Necropsy, 'no abnormalities of interest'.

4. Lachmann (1941), Case 59. Danish man aged 40. Tetany on exertion since 19 years old, markedly seasonal. Depression and fatigue. Small, broad-shouldered, with short extremities. Height 4 ft. 10 in. Cataracts. Cerebral calcification. Metacarpals, metatarsals and phalanges short and plump, especially fourth metacarpals. Styloid process of ulna detached. Serum calcium 6·3 mg. per 100 ml., phosphorus 5·9 mg. per 100 ml. Response to A.T.10.

The above three cases reported as 'idiopathic hypoparathyroidism'.

5. Albright, Burnett, Smith and Parson (1942), Case 1. Russian Jewish woman aged 28. Fits from age of 12.

Irregular menses. Severely mentally retarded. Round face, short, fat. Height 4 ft. 3 in. Index finger longer than middle. Metacarpals and metatarsals short and stubby. Whole skeleton dense. Areas of soft tissue calcification in extremities. Serum calcium 6·4 mg. per 100 ml. phosphorus 6·2 mg. per 100 ml. Parathyroid hormone 74 ml. in 12 days administered with no effect. Response to large doses of A.T.10 (15 mg. daily).

Reported as 'pseudo-hypoparathyroidism'.

6. Albright, Burnett, Smith and Parson (1942), Case 3. American boy aged 3¼ years. Choking spells and wheezing, aged 2 years. Fits from 2½ years. Obese from infancy. Round faced, stocky. Small, hard, calcified masses to be felt in subcutaneous tissues of trunk and extremities. Bones radiologically normal. Abductor palsy of larynx led to tracheotomy. Serum calcium 7·1 mg. per 100 ml., phosphorus 10 mg. per 100 ml. Given 1,700 U.S.P. units 'parathormone' in five days without effect. Response to large doses of A.T.10 (20-25 mg.). Laryngeal function returning.

Reported as 'pseudo-hypoparathyroidism'.

7. Sprague, Haines and Power (1945). American woman of 33 years. Convulsions from 14 years. Round face, short, thick set. Agenesis of first, fourth and fifth metacarpals. Intracranial calcification. Calcification of abdominal wall. Serum calcium 4·6 mg. per 100 ml., phosphorus 5·3 mg. per 100 ml. No effect from parathyroid hormone in large doses. Response to A.T.10 and calciferol.

Reported as 'pseudo-hypoparathyroidism'.

8. Richardson (1946). English boy aged 16. Fits from 1½ years. Tetany from age 5. Short stature. Mental retardation. Rather fat face. Cataracts. Intracranial calcification. Short, squat metacarpals with flecks of soft tissue calcification around them. Serum calcium 4·1 mg. per 100 ml., phosphorus 9·9 mg. per 100 ml. Ten days of 'parathormone' 60 units daily failed to control tetany or to influence serum electrolytes. Slow response to calciferol.

Reported as 'chronic idiopathic hypoparathyroidism'.

9. Scott and Temple (1949). American boy of 9 years. Calcified nodules appeared in the skin when aged 2 months. Rapid gain in weight. Grossly obese; weighed 67 lb. at 14 months. Convulsions at 5 years. Very backward mentally. Radiograph shows extensive calcification in the skin. Biopsy, bone formation. Serum calcium 7·1 mg. per 100 ml. Serum phosphorus 13·1 mg. per 100 ml.

Reported as 'osteoma cutis', and suggested as a case of pseudo-hypoparathyroidism by Bakwin, Gorman and Ziegra (1950).

10. Peterman and Garvey (1949). American girl of 12. Laryngospasm from infancy. Cramps from 2 years old. Recent fits. Mentally backward. Round face. Height 4 ft. 6 in., weight 101 lb. Cerebral calcification. Subcutaneous calcification. Generalized osteoporosis. Serum calcium 6·6 mg. per 100 ml., phosphorus 12 mg. per 100 ml.

Reported as 'pseudo-hypoparathyroidism'.

11. Selye (1949), Case 1. American girl of 8½ years. Fits. Stocky figure, round face. Peculiar hands; index finger longest, all metacarpals except second shortened. Latent tetany. Interstitial calcification at the wrist. Premature closure of elbow epiphyses and bowing of the radius. Spur formation on the tibia. Serum calcium 4·5 mg. per 100 ml., phosphorus 10·2 mg. per 100 ml. Response to A.T.10.

12. Selye (1949), Case 2. Mother of Case 1 *supra*. 'A mild form of the disease.' Shortening of fingers 4 and 5, with bowing of the radius. Soft tissue calcification. No tetany or epilepsy. Serum calcium 10·8 mg. per 100 ml., phosphorus 6·2 mg. per 100 ml.

The last two cases reported as 'pseudo-hypoparathyroidism'.

13. Schüpbach and Courvoisier (1949). Swiss man of 35 years. Round faced, short. Height 4 ft. 8 in. Stupid. Mild thyroid enlargement. Short thick fingers. Cataracts. Cerebral calcification. Hyperostosis of skeleton. Short metacarpals. Serum calcium 4·2 mg. per 100 ml., phosphorus 6·8 mg. per 100 ml. Response to A.T.10.

Reported as a case intermediate between spontaneous hypoparathyroidism and pseudo-hypoparathyroidism.

14. Gsell (1950). German man of 47 years. Tetany since 8 years. Dwarfism; mild adiposity. Height 4 ft. 8 in. Slightly retarded mentally. Cataracts. Intracranial calcification. Psoriasis. Skeletal osteoporosis. Short metacarpals. Serum calcium 6 mg. per 100 ml. Some rise in serum calcium in response to parathyroid hormone.

Reported as 'chronic idiopathic tetany with psoriasis'.

15. Uhlemann (1950), Case 1. German girl aged 20 years. Anxiety attacks and stridor from age of 15 years. Red hair. Dwarfism and adiposity. Height 4 ft. 5 in., weight 116 lb. Cretinoid appearance. Intelligence at lower limit of normal. Convergent squint. Poorly developed secondary sex characters. Cataracts. Striking shortness of fingers. Metacarpals 4 and 5 and phalanges short. Serum calcium 5·8 mg. per 100 ml. Response to A.T.10.

16. Uhlemann (1950), Case 2. German girl aged 9½ years. Sister of Case 1 *supra*. Height 4 ft. 2 in., weight 44 lb. Short plump fingers. Metacarpals 2 to 5 short and plump, with premature fusion of epiphyses. Terminal phalanges broad. Serum calcium 7·8 mg. per 100 ml. Response to A.T.10.

Both the above cases reported as 'familial idiopathic tetany'.

17. Elrick, Albright, Bartter, Forbes and Reeves (1950), Case 2. Italian girl aged 17 years. Main complaint of excessive sleepiness. Obesity and short stature. Height 4 ft. 3 in., weight 146 lb. Mentally retarded. Short fingers and toes; index as long as middle finger. Multiple areas of soft tissue calcification. Serum calcium 6 mg. per 100 ml., phosphorus 6 mg. per 100 ml.

Reported as 'pseudo-hypoparathyroidism'.

18. Alexander and Tucker (1950). American man aged 49 years; married with two normal children. Fat from infancy. Short, stocky. Height 4 ft. 11 in., weight 145 lb. Limbs short relative to trunk. Cataracts. Parkinsonism. Intracranial calcification. Subcutaneous plaques of bone, with limitation of movement at many joints. Serum calcium 6·8 mg. per 100 ml., phosphorus 4·5 mg. per 100 ml. Response to A.T.10.

Reported as 'pseudo-hypoparathyroidism'.

19. Bakwin, Gorman and Ziegra (1950). American girl aged 16 years. Diagnosed aged 8 as chondrodystrophy. Convulsions from age 14. Short, with short arms. Height 4 ft. 2 in. Short fingers of irregular length, asymmetrical on the two sides. Mentality lower limit of normal. Metacarpals short and broad, except right second and left third. Phalanges of feet abnormal. Ulnae and radii broad and gnarled; fibulae bent. Serum calcium 6·7 mg. per 100 ml., phosphorus 7·0 mg. per 100 ml. Response to both A.T.10 and 'calciferol'.

Reported as ' pseudo-hypoparathyroid tetany'.

20. Bishop and de Mowbray (1951). English girl of 18 years. Tetany from 6 years old. Always under-sized. Round faced, dwarfed, somewhat obese. Height 4 ft. 7 in., weight 102 lb. Short hands. Shortening of fourth and fifth metacarpals and of fourth metatarsals, and terminal phalanges of fingers. Marked mental retardation. Intracranial calcification. Soft tissue calcification. Bowing of tibiae, with osteophyte formation. Serum calcium 6 mg. per 100 ml., phosphorus 4·2 mg. per 100 ml. Response to A.T.10.

Reported as 'pseudo-hypoparathyroidism'.

21. Reynolds, Jacobson, Edmondson, Martin and Nelson (1952). American negro male aged 29 years. Mental retardation from childhood. Fits from age 8. Cataracts from 8 years. Subcutaneous nodules from 10 years. Short, well proportioned. Height 5 ft., weight 116 lb. Round face. Early Parkinsonism. Calcification of basal ganglia. Generalized demineralization of skeleton. Metacarpals and phalanges short and thick, chiefly fifth metacarpals. Flattening of femoral heads. Serum calcium 5·8 mg. per 100 ml., phosphorus 5·4 mg. per 100 ml. Response to A.T.10.

Reported as 'pseudo-hypoparathyroidism'.

22. Bille (1952). Swedish girl of 9 years. Obesity and short stature from early infancy. Convulsions from 7 years old. An uncle was an imbecile of similar physique, but with normal serum calcium. Short (4 ft. 1 in.), thick-set, round face. Index finger longer than the others. Intelligence quotient 71. Shortness of all metacarpals except second. Subcutaneous calcification around ankle. Serum calcium 6 mg. per 100 ml., phosphorus 12·5 mg. per 100 ml. Ellsworth-Howard test (intramuscular 'paroidin' 200 units) negative. Some inconstant rise in serum calcium in response to several injections of parathyroid hormone. Trial of A.T.10 in small (5 mg.) doses produced little effect.

23. Azerad, Gatha and Raverdy (1953). French woman, aged 24. Always obese. Fits from 7 years old. Sister had fits and cataracts, and died at 20 years in an unexplained coma. At 7 years early papilloedema was noticed, and an accompanying loss of vision appeared to be accentuated by a course of arsenical treatment. Soon after cataracts appeared, and in the early 20s acute glaucoma necessitated enucleation of the left eye. The same condition then appeared on the right. Short (4 ft. 3 in.), stumpy build with a round face. Short extremities. Index finger longer than the others. Subcutaneous calcification of face. Teeth irregularly erupted and spaced. Mentality childish; very dependent on her mother. Basal metabolic rate 20%. Radio-active iodine uptake normal. Serum calcium 8·6 mg. per 100 ml., phosphorus 5·5 mg. per 100 ml. Radiographs of bone show marked general decalcification. Ellsworth-Howard test negative.

For details of the following unpublished case of pseudo-hypoparathyroidism we are indebted to Dr. W. W. Payne.

English boy aged 7 years. At 6 months old calcified lumps in the skin began to appear and were distributed widely over the body. Biopsy of one of these revealed ectopic bone. Stout infant, backward in speaking, Undescended testicles. Serum calcium 6·3 mg. per 100 ml., phosphorus 7·2 mg. per 100 ml. At 6½ years, weight 37 lb., height 3 ft. 8 in. Intelligence quotient 60. Some response was observed to 'parathormone' 40 U.S.P. units intravenously, notably a twofold increase in urinary phosphorus excretion between the sixth and ninth hours after injection. Good therapeutic response to calciferol.

For details of the following case of steatorrhoea, which is referred to in the text, we are indebted to Dr. A. I. Cheyne.

Man aged 30. Well until nine months before admission, when paraesthesiae in hands, transitory oedema of the ankles and weakness developed, but lasted only a short time. Some months later he developed carpo-pedal spasms and on examination was found to have latent tetany. He was otherwise in vigorous health, and nothing to account for his tetany was found in his past history, in his urine, or in bone radiographs, but a three-day stool analysis showed a fat excretion of 11 g. per day. His serum values for calcium and phosphorus were 6·2 and 6·3 mg. per 100 ml. respectively. An Ellsworth-Howard test gave a negative result. After four days of 150 U.S.P. units 'parathormone' daily serum calcium and phosphorus values were, respectively, 6·0 and 5·0 mg. per 100 ml.

CHRONIC IDIOPATHIC HYPOPARATHYROIDISM ASSOCIATED WITH MONILIASIS

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From the Royal Aberdeen Hospital for Sick Children

(RECEIVED FOR PUBLICATION MAY 12, 1954)

Idiopathic hypoparathyroidism is probably less rare than is commonly thought. Steinberg and Waldron (1952) in a comprehensive review of the literature collected 51 cases and added one of their own, but they did not include several reported cases whose serum inorganic phosphorus did not exceed 5·0 mg. %. Few reports have come from this country. Humphreys (1939), Himsworth and Maizels (1940), Jordan and Kelsall (1951) each report one case, and de Mowbray, Llewellyn Smith and Symonds (1954) add three more. In Steinberg's 52 collected cases symptoms had appeared by the age of 12 years in 50%, but symptoms frequently persisted for several years before the diagnosis was made. Convulsions occurred in more than 50% of the cases, and an earlier diagnosis might be made if idiopathic hypoparathyroidism were considered in all children presenting with convulsions.

In 10 reported cases fungus infections have been found along with parathyroid deficiency. Thorpe and Handley (1929), Sevringhaus and St. John (1943), Talbot, Butler and MacLachlan (1943), Gotta and Odoriz (1948), Collins-Williams (1950) all report one case, and Sutphin, Albright and McCune (1943) add five cases, three in siblings.

In the case reported here chronic parathyroid insufficiency was associated with chronic moniliasis.

Case Report

In August, 1953, a girl aged 11 years was admitted to hospital for investigation of convulsions. She was an only child. Her mother was healthy but her father had been killed shortly before her birth. In 1946, at the age of 4½ years, she had an acute illness with pains in the legs and arms. She was admitted to an infectious diseases hospital as a case of poliomyelitis. On examination she had some carpopedal spasm which passed off rapidly. Trousseau's and Chvostek's signs were not present. The serum calcium level was 7·8 mg. %. She had a thrush infection of the mouth. There was no evidence of poliomyelitis and the final diagnosis was alkalosis.

Soon after discharge from hospital she developed ptosis of both eyelids. Photographs taken before her first admission to hospital show that she had no ptosis then. About March, 1947, the nails of the right hand became rigid and thickened, and cracks appeared at the angles of the mouth. In January, 1951, the nails of the left hand and of the toes became similarly affected. In May, 1951, she had three typical grand mal fits over a period of two days. In June, 1951, she was re-admitted to hospital for investigation of these fits.

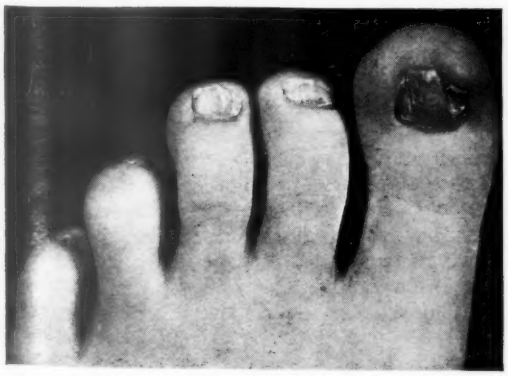


FIG. 1A.

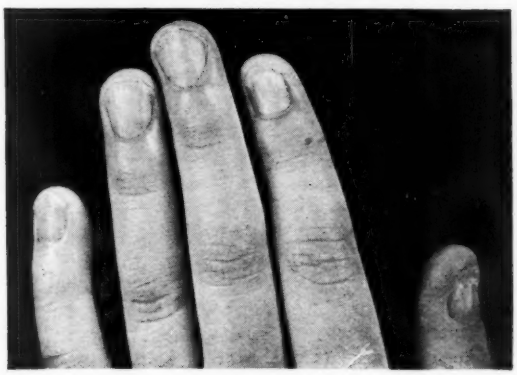


FIG. 1B.

FIGS. 1A and B.—Photographs showing ridging and cracking of finger and toe nails.

On examination she was a well built, well nourished girl with ptosis of both eyelids. The angles of the mouth were cracked and the mucous membrane was heaped up into plaques, the nails were ridged and brittle, and the thumb nail beds were inflamed. No other abnormalities were noted. The cerebrospinal fluid was normal, and the blood Wassermann reaction was negative. A radiograph of the skull showed a small area of calcification in the left cerebrum in the region of the basal ganglia, but the significance of this was not appreciated. The lesions of the nails and mouth were ascribed to a metabolic upset, and she was discharged on treatment with a multi-vitamin preparation.

She remained well until June, 1953, when she had two convulsions during dental extraction. These were accompanied by carpopedal spasm.

In August, 1953, she was again admitted to hospital for investigation.

She was a tall, well nourished girl. Her skin was smooth and her hair was dry but not scanty. The finger and toe nails were ridged and broken (Fig. 1), and the mucous membrane at the angles of the mouth was cracked and thickened (Fig. 2). She had already

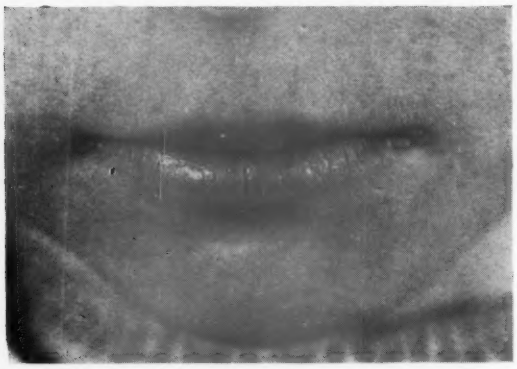


FIG. 2.—Photograph showing thrush lesions at angles of the mouth.

lost all four six-year molars, and the lower incisors were carious, but radiographs showed that the roots of erupted and unerupted teeth were all normal. Ptosis of the eyelids was still present. Chvostek's and Trousseau's signs were present on most occasions but at times negative responses were elicited. Urine examination gave specific gravity readings up to 1028, no abnormal substances were found in any specimen, but Sulkowitch's test for calcium was repeatedly negative. A swab from the angles of the mouth grew *Candida albicans*. Serum calcium was 6·7 mg. % and serum phosphate 7·6 mg. %. A radiograph of the skull now showed bilateral symmetrical calcification in the region of the basal ganglia (Fig. 3). Radiographs of the long bones showed no abnormality. An electrocardiogram showed a prolonged Q-T interval of 0·36 second at a heart rate of 100 per minute. The Ellsworth Howard test gave a marked rise in the urinary excretion of phosphate following the intravenous injection of parathormone (Fig. 4). On the history of chronic tetany

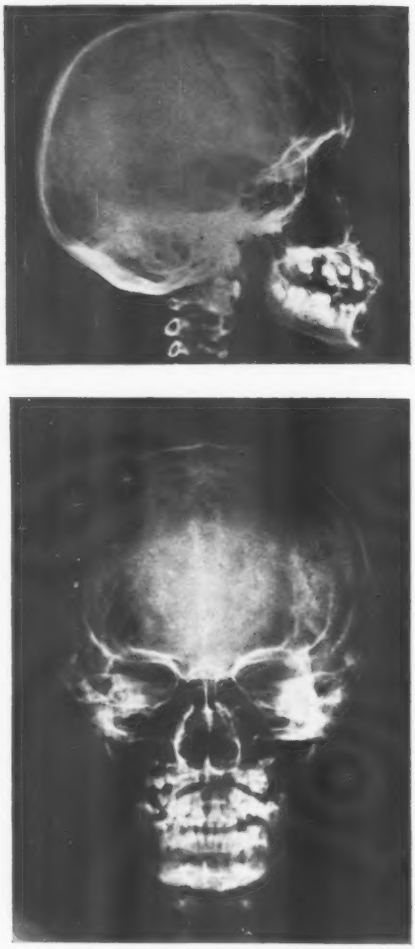
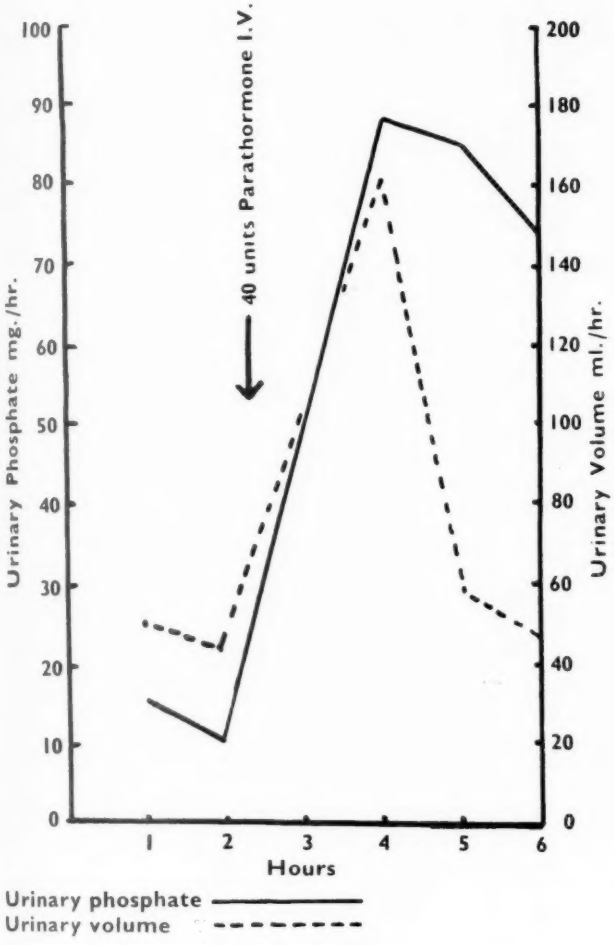


FIG. 3.—Radiograph of skull showing calcification in the region of the basal ganglia.

and convulsions, the low serum calcium, high serum phosphate readings, the absence of renal insufficiency, the normal bones found in radiographs and the positive response to the Ellsworth Howard test, the diagnosis of chronic idiopathic hypoparathyroidism was made.

Treatment was started with A.T.10 (dihydrotachysterol). Two doses of 0·5 ml. were given with a two-day interval between doses, and the dose was then increased to 1·0 ml. every second day. After four days on treatment small amounts of calcium began to appear in the urine. After three weeks' treatment A.T.10 was discontinued and treatment with 25,000 units of 'calciferol' daily, and 60 grains of calcium lactate three times daily, was started. On this treatment she continued to excrete calcium, the serum calcium level rose to 8·18 mg.%, but the phosphate still remained high at 8·6 mg. %. Within a few weeks of starting treatment the child became much brighter and very talkative, whereas previously she had been very quiet and a little morose. On treatment with vitamin D and calcium by mouth, she remains well and continues to excrete calcium in the urine.

FIG. 4—Graph illustrating the rise in the urinary excretion of phosphate after the intravenous injection of parathormone



Comment

The frequency with which monilial infection has been reported in idiopathic hypoparathyroidism indicates that it is more than a chance finding. It has not been reported in parathyroid deficiency following thyroidectomy, and in some cases has preceded the appearance of symptoms of hypoparathyroidism.

It seems unlikely that the fungus infection is responsible for depression of parathyroid activity, but there may be some factor which depresses the parathyroids and also encourages fungus infections.

The occurrence of ptosis following the first episode of tetany in this child has not been explained. The changes in the nails may be due to monilial infection, or to lack of calcium, but there is no doubt that the mouth lesions have been due to chronic moniliasis.

Summary

A case of chronic idiopathic hypoparathyroidism associated with moniliasis is reported.

REFERENCES

Collins-Williams, C. (1950). *Pediatrics*, **5**, 998.
Gotta, H. and Odoriz, J. B. (1948). *J. clin. Endocr.*, **8**, 674.
Himsworth, H. P. and Maizels, M. (1940). *Lancet*, **1**, 959.
Humphreys, H. F. (1939). *Proc. roy. Soc. Med.*, **32**, 633.
Jordan, A. and Kelsall, A. R. (1951). *Arch. intern. Med.*, **87**, 242.
Mowbray R. R. de, Smith, S. H. Llewellyn and Symonds, W. J. C. (1954). *Brit. med. J.*, **1**, 903.
Sevringhaus, E. L. and St. John, D. (1943). *J. clin. Endocr.*, **3**, 635.
Steinberg, H. and Waldron, B. R. (1952). *Medicine, Baltimore*, **31**, 133.
Sutphin, A., Albright, F. and McCune, D. J. (1943). *J. clin. Endocr.*, **3**, 625.
Talbot, N. B., Butler, A. M. and MacLachlan, E. A. (1943). *J. clin. Invest.*, **22**, 583.
Thorpe, E. S. and Handley, H. E. (1929). *Amer. J. Dis. Child.*, **38**, 328.

COMPLEMENTARY FEEDS—BY SPOON OR BOTTLE?

BY

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(RECEIVED FOR PUBLICATION APRIL 14, 1954)

It has often been stated that if complementary feeds are given during the period when lactation is established they should only be given by spoon (Naish, 1948, 1952, 1953).

Naish wrote:

> 'Once a baby is introduced to the bottle, there is a very great danger that it will either refuse the breast entirely, or work the breast insufficiently, so that the milk supply is inadequately stimulated. This happens because the action required to get milk from the rubber teat is quite different and decidedly easier. . . . To maintain breast feeding, it is absolutely essential that all complement should be given with a spoon.'

Evans and Mac Keith (1951) wrote:

> 'Extra feeds may be given by spoon or bottle. The former is preferred, as sometimes infants who have had a bottle refuse to take the breast.'

It takes much longer to give complementary feeds by spoon, and it was therefore thought worth while to conduct a simple controlled experiment in order to determine whether this method of giving complementary feeds is really necessary.

Method of Study

At the Jessop Hospital for Women at Sheffield complementary feeds are only given on the instruction of the Paediatric Registrar. When it was thought necessary to give complementary feeds, the random sampling method, with the usual packets of sealed envelopes, was used to determine whether the complementary feeds should be given by spoon or bottle. Only full-term babies were used for the experiment, and none of these were excluded. After discharge from hospital, on approximately the ninth day in most cases, all babies who still needed complementary feeds were given them by bottle. The aim was simply to determine whether the use of a bottle for giving complementary feeds had an adverse effect on the establishment of lactation.

The following records were kept on proformas: the weight at birth, the weight on alternate days while in hospital, the type of feeding on discharge and at 1 month (fully breast fed, complementary feeds, artificially fed), the weight at 1 month and the speed of weight gain between the time of discharge and the follow-up visit at 1 month, with reasons for giving complementary feeds, the quantity of complementary feeds given and the days on which they were given, the parity of the mother and the feeding history in previous pregnancies. In all, 100 babies were studied, 50 being given their complementary feeds by spoon and 50 by bottle.

Results

Comparability of the Two Groups. Thirty-six mothers in each group were primiparae. The average birth weight in group A (complementary feeds given by bottle) was 6 lb. 7 oz., and in group B (complementary feeds given by spoon) 6 lb. 6 oz. The range was as follows:

Birth Weight	Group (Number of Cases) A	B
5 lb. 8 oz. to 6 lb. 15 oz.	20	15
7 lb. 0 oz. to 8 lb. 7 oz.	20	30
8 lb. 8 oz. or more	10	5

There was no difference between the two groups with regard to the quantity of food given as complement or the number of days after birth before complementary feeds were given.

TABLE 1

TYPE OF FEEDING IN RELATION TO METHOD OF GIVING COMPLEMENTARY FEEDS

Type of Feeding	On Discharge (%) A* (Bottle)	On Discharge (%) B (Spoon)	At 1 Month (%) A	At 1 Month (%) B
Fully breast-fed ..	56	62	50	48
Complementary feeds	30	20	16	14
Entirely artificially fed	14	18	34	38

* 50 babies in each group.

TABLE 2

TYPE OF FEEDING AT 1 MONTH RELATED TO DURATION OF COMPLEMENTARY FEEDING IN THE FIRST 10 DAYS

Duration of Complementary Feeding	Proportion Fully Breast-fed at 1 Month	
	Group A (Bottle)	Group B (Spoon)
4 days or more	9/24	5/19
3 days	9/15	10/19
1 or 2 days	7/11	9/12

TABLE 3

TYPE OF FEEDING AT 1 MONTH RELATED TO QUANTITY OF COMPLEMENTARY FEEDS IN FIRST 10 DAYS

Quantity of Complementary Feed per Day	A* (Bottle)			B* (Spoon)		
	Fully Breast Fed	Complementary Feed	Artificially Fed	Fully Breast Fed	Complementary Feed	Artificially Fed
Less than 10 oz.	10	5	2	7	1	4
10 oz. or more	15	2	16	17	7	14

* 50 babies in each group.

Relationship of Method to Incidence of Breast Feeding. Table 1 shows that the incidence of breast feeding in the two groups both on discharge and at 1 month was much the same. In group A (bottle) 43 of the 50 babies were fully or partially breast fed on discharge, and 41 of the 50 at 1 month. The corresponding figures in group B (spoon) were 41 and 31. Tables 2 and 3 show that the duration of complementary feeding (in the first 10 days) and the quantity of complementary feed given had no effect on the relative results in the two groups.

There was no evidence that the method of giving the complementary feeds bore any relation to the amount of milk which mothers produced. The mean test feed (including milk expressed) on the eighth day in the case of mothers of babies in group A (bottle) was 14 oz. as compared with 12 oz. for group B (spoon). The average weight gain between the time of discharge and the time of the first follow-up visit at approximately 1 month was analysed in the case of those fully breast fed when followed up. The average weekly weight gain in that period for the 25 babies in group A was 8 oz. as compared with 6·4 oz. for the 24 babies in Group B.

None of these differences is statistically significant.

Discussion

It will be seen that this simple controlled investigation showed that the giving of complementary feeds by spoon instead of by bottle presented no advantage in relation to the incidence of breast feeding and the effect on the mother's breast milk production. The very slight differences in the two groups, though not of statistical significance, were in favour of the bottle-fed group.

It has been argued that a good reason for advocating that all complementary feeds should be given by spoon instead of by bottle lies in the fact that it takes longer to give them by spoon, and this deters nurses from giving complementary feeds unnecessarily. It seems that the unnecessary use of complementary feeds could be better prevented by proper teaching and supervision of nurses than by a method which merely wastes their time.

Summary

A controlled investigation was carried out in order to compare the effect on the establishment of lactation of giving complementary feeds, where indicated, by spoon and by bottle. There were 50 babies in each group, chosen by random sampling. The experiment failed to reveal any advantage in using the more time-consuming method of giving the feeds by spoon.

Our thanks are due to the Matron of the Jessop Hospital, Miss J. W. Taylor, and to all the sisters and nurses who so willingly cooperated in this investigation. We also wish to thank Dr. T. Colver, for allowing us to include his patients in the series.

REFERENCES

Evans, P. and Mac Keith, R. (1951). *Infant Feeding and Feeding Difficulties*. London.

Naish, F. C. (1948). *Breast Feeding*. London.

—— (1952). In *Child Health*, ed. Moncrieff, A. and Thompson, W. A. R., p. 211. London.

—— (1953). *Brit. med. J.*, **1**, 1442.

THE BONNEVIE-ULLRICH SYNDROME

BY

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From the Royal Hospital for Sick Children, Edinburgh

(RECEIVED FOR PUBLICATION MAY 19, 1954)

Turner's syndrome, the association of webbing of the neck, cubitus valgus and infantilism, is well recognized. Much less attention, however, has been paid to a condition occurring in infancy characterized by symmetrical webbing of the neck and lymphangiectatic oedema of the extremities as well as other features, and is termed the Bonnevie-Ullrich syndrome. This condition has been extensively studied on the continent of Europe, and Ullrich (1949) now believes that the bilateral symmetrical form of this condition is identical with Turner's syndrome.

There appears to be no report of cases of the Bonnevie-Ullrich syndrome in Great Britain although James (1952) has described a case of Turner's syndrome in a male infant. The following case therefore is presented in the hope that further interest may be stimulated in this unusual congenital malformation.

Case Report

M.V., a girl, was born at term in a Stirlingshire maternity home on May 21, 1953, after an uneventful pregnancy. The birth weight was 3·6 kg. (8 lb.). She was the third child of healthy, unrelated parents. The family history appeared irrelevant.

After five weeks of normal progress she began to vomit frequently, and, because of the projectile nature of these vomits, she was admitted to the Royal Hospital for Sick Children, Edinburgh, on July 28, aged 2 months.

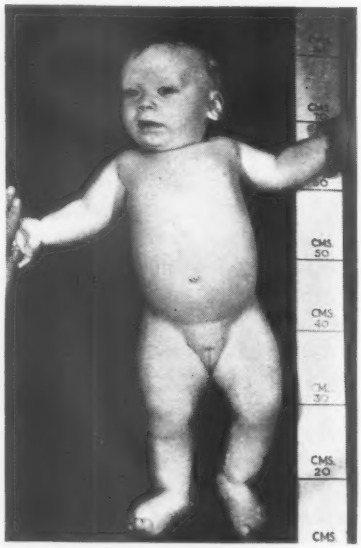

FIG. 1.—M.V., aged 8 months.

The presence of congenital hypertrophic pyloric stenosis was confirmed and the condition was relieved successfully by Rammstedt's operation on August 4.

It was noted on admission that she was a well nourished healthy looking infant despite the vomiting. In addition, certain unusual features were present. She had well developed epicanthic folds, a low nasal bridge and a cavernous haemangioma which deformed the lobe of the left ear (Fig. 1). There was latent webbing of the neck which could be easily drawn out (Fig. 2) and the skin of the upper back was unusually loose. There was a low nuchal hairline. An outstanding feature was the marked non-pitting oedema of the feet (Fig. 3) and, to a lesser extent, of the hands. The nipples were small and widely separated. Cubitus valgus deformity was present. The

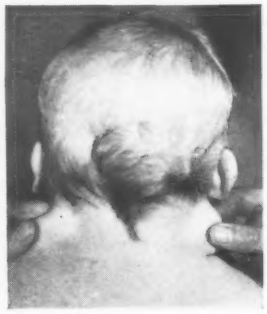

FIG. 2.

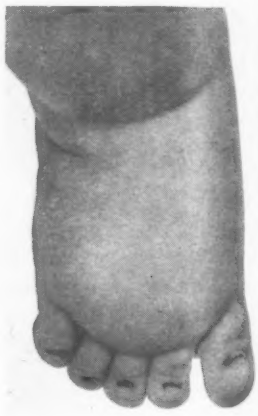

FIG. 3.

finger and toe nails were deformed. Muscle tone and joint motility were considered normal. No evidence of congenital heart disease was found, the femoral pulses, the heart outline radiologically and the electrocardiogram being normal.

The external genitalia were normal for the child's age.

Radiology showed normal skull films without increased digital impressions. The spine views showed no vertebral anomalies. The long bones appeared to be broad at the epiphyses but assessment at this age was difficult. The extremities showed no bony abnormality.

The blood examination, the plasma proteins and the urine were all normal and the Wassermann reaction was negative.

The child has been seen at regular intervals since the operation for pyloric stenosis and her progress has been normal. On February 1, 1954, she was admitted for further assessment. The oedema was still well marked although less tense and there had been no change in the latent webbing of the neck. The child's measurements at the age of 8 months were as follows: Length, 65·5 cm. (25¾ in.); sitting height, 42 cm. (16½ in.); occipito-frontal circumference, 45 cm. (17¾ in.); chest circumference, 49 cm. (19¼ in.); abdominal circumference, 46·5 cm. (18¼ in.); weight, 8·8 kg. (19½ lb.).

An estimation of the 24-hour excretion of urinary gonadotrophins showed less than 6 mouse units of the follicle-stimulating hormone.

Discussion

The combination of webbing of the neck and lymphangiectatic oedema was commented upon by Ullrich in 1930. He described a 'Typisches Kombinationsbild Multipler Abartungen' which included in addition deformities of the ears, hypoplasia of the nipples, syndactyly, dystrophic nails, muscle defects and motor disturbances in the cranial nerve area. His report included four cases observed personally and 15 from the literature.

In 1938, after studying the work of Bonnevie (1934), which demonstrated the formation of multiple anomalies in an abnormal strain (my) of the house mouse, by 'wandering blebs' of cerebrospinal fluid acting in the early embryo, Ullrich postulated that such a mechanism might also be responsible for the syndrome which he had described. He quoted reports of 'stillborn foetuses showing massive oedema of the neck region of a form like that occurring in "my" mouse embryos'.

The condition became known as the Bonnevie-Ullrich syndrome, and a number of cases have been reported in German, Swiss, French and Italian journals and were reviewed by Rossi and Caflisch (1951).

Meanwhile in 1938, Turner in America had described a syndrome characterized by the triad of infantilism, congenital webbed neck and cubitus valgus. As this was subsequently considered primarily an endocrine disorder, further study of the syndrome was directed principally at the associated hypogonadism.

After the Second World War when the interchange of scientific knowledge between America and the European continent was resumed Ullrich (1949) reassessed his original conception of the Bonnevie-Ullrich syndrome, and he concluded that it could no longer be reconciled with an unqualified theory of wandering cerebrospinal fluid blebs.

The symmetrical form, which was characterized by bilateral webbing of the neck, showed the most marked discrepancies, both because of its symmetrical nature and its pronounced predilection for the female sex. The ratio in infancy was nine females to one male, and at all ages, four females to one male. Furthermore, he considered that the symmetrical form of the Bonnevie-Ullrich syndrome and Turner's syndrome should be classified together.

The characteristics of the symmetrical form were defined by Ullrich (1949) as follows: (1) Webbing of the neck, which at birth was represented by oedematous swelling, and oedema of the extremities which on regression left the skin 'too loose'; (2) moderate dwarfism, hypoplasia of the nipples and sexual immaturity; (3) a low hairline at the nape of the neck and deep-set ears which might show certain degenerative characteristics; (4) frequently epicanthic folds and triangular appearance of the mouth because of the deep-set corners; (5) frequently short and perpendicular nails. (6) There were generally no other web formations nor was there any cranial nerve abnormality. Mental development was normal. (7) Skeletal deformities included an arched palate and cubitus valgus. On radiological examination, mushrooming of the epiphyses and increased digital impressions on the skull were sometimes present. (8) Apart from aplasia of the gonads, involvement of internal organs was rare, although cardiac abnormality such as coarctation of the aorta had been described.

In the case reported above there were sufficient of these features to warrant a diagnosis of the symmetrical form of the Bonnevie-Ullrich syndrome. At her present age there is no evidence of retarded development. An unusual feature of this case is the hypertrophic pyloric stenosis. (This association has not been reported previously, but in one of the cases described by Guinand-Doniol (1947) there was a duodenal stenosis.)

Elevation of the urinary gonadotrophins in patients with primary hypogonadism is not usually found before the age of 10 to 12 years. Silver and Kempe (1953), however, reported an increased level of follicle-stimulating hormone in the urine of a girl of 2 years 8 months who presented the characteristic features of the symmetrical Bonnevie-Ullrich syndrome, ovarian agenesis being confirmed by laparotomy at the age of 4 years.

Although Ullrich had stated that the Bonnevie-Ullrich and Turner's syndromes were associated, it is not clear from a study of the many reports whether all cases of the former have been proved to have hypogonadism. The lack of reports of the Bonnevie-Ullrich syndrome in the English literature compared with the number of cases of Turner's syndrome would suggest that not all those with the

latter condition had peripheral lymphangiectatic oedema in infancy. Further evidence on this point should be easily obtainable from adult endocrinological clinics.

Similarly, ovarian agenesis and webbing of the neck are not invariably associated. It is estimated that a third to a half of the recorded cases of hypogonadism have webbed necks and at least a third of cases of webbing of the neck show hypogonadism (Skjelbred, 1953).

The aspects of webbing and of hypogonadism receive different attention in the European and the American literature. The European attitude, usually based on a young age group, is typified by the association of five conditions in which webbing occurs under the title of the pterygium syndrome (Rossi and Caflisch, 1951). The conditions are (1) bilateral Ullrich syndrome, (2) dystrophia brevicolli congenita (including the Klippel-Feil deformity), (3) pterygonuchal infantilism (Turner's syndrome), (4) unilateral Ullrich syndrome, and (5) congenital pterygoarthromyodysplasia.

Rossi and Calflisch concluded from the aetiology and from the analogy with other syndromes that the pterygium syndrome was hereditary.

American authors, on the other hand, regard Turner's syndrome as a sub-division of a wider complex in which decreased stature is associated with primary gonadal insufficiency and which is to be distinguished from pituitary dwarfism (Albright, Smith and Fraser, 1942). The decreased stature is generally considered to be primordial rather than of endocrine origin. The majority of American studies are with adult patients.

Finally, it would appear that the time has now arrived when eponyms should be abandoned and a clinical description substituted. It is suggested that pterygolymphangiectasia would describe the Bonnevie-Ullrich syndrome which could subsequently become pterygolymphangiectatic infantilism when gonadal hypoplasia was established.

Summary

A typical case of the symmetrical form of the Bonnevie-Ullrich syndrome with, in addition, congenital hypertrophic pyloric stenosis, is recorded.

The American and European literature concerning the Bonnevie-Ullrich syndrome and its relationship to Turner's syndrome is discussed.

A new name for the Bonnevie-Ullrich syndrome is suggested.

We wish to thank Dr. D. N. Nicholson for permission to publish this case and we are grateful to Professor R. W. B. Ellis for his helpful criticism.

References

Albright, F., Smith, P. H. and Fraser, R. (1942). *Amer. J. med. Sci.*, **204**, 625.
Bonnevie, K. (1934). *J. exp. Zool.*, **67**, 443.
Guinand-Doniol, J. (1947). *Ann. paediat., Basel*, **169**, 317.
James, T. (1952). *Edinb. med. J.*, **59**, 344.
Rossi, E. and Caflisch, A. (1951). *Helv. paediat. Acta*, **6**, 119.
Silver, H. K. and Kempe, C. H. (1953). *Amer. J. Dis. Child.*, **85**, 523.
Skjelbred, P. (1953). *Archives of Disease in Childhood*, **28**, 8.
Turner, H. H. (1938). *Endocrinology*, **23**, 566.
Ullrich, O. (1930). *Z. Kinderheilk.*, **49**, 271.
—— (1938). *Klin. Wschr.*, **17**, 185.
—— (1949). *Amer. J. hum. Genet.*, **1**, 179.

POST-NATAL CHANGES IN THE INTRA-ABDOMINAL UMBILICAL VEIN

BY

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(RECEIVED FOR PUBLICATION APRIL 12, 1954)

Recent investigations of the birth changes in the foetal circulation indicate that certain channels, namely, the ductus arteriosus, ductus venosus and extra-abdominal umbilical vessels, are quickly closed by the contraction of their muscular walls (Barclay, Franklin and Prichard, 1944). This immediate functional closure is followed by an anatomical obliteration which takes place during the first few weeks or months of life (Scammon and Norris, 1918; Kennedy and Clark, 1941). Little appears to be known regarding the functional response to birth changes of the intra-abdominal umbilical vein, but Barclay *et al.* (1944) note the following facts.

First, that there is a marked difference between the structure of the intra- and extra-abdominal parts of the umbilical vein: the former is thin-walled with only a small amount of smooth muscle, whereas the latter has a very thick muscular wall. Second, that the intra-abdominal umbilical vein is much reduced in calibre and contains little or no blood when examined some time after rupture of the cord.

Sidbury (1923) first used the umbilical vein as a transfusion route (in infants suffering from icterus gravis neonatorum) by inserting a needle into the extra-abdominal umbilical vein just beyond the ligature on the cord. He found no clot in the vein and attributed this to the delay in clotting which is a characteristic of this condition. Diamond (1947) elaborated this method by severing the umbilical cord, some half-inch from the abdominal wall, and inserting a polythene catheter of 1 mm. internal diameter directly into the intra-abdominal umbilical vein. This technique is now the standard one for performing exchange transfusions in icterus gravis neonatorum and may be employed for as long as six days after birth (Diamond, 1954). When the cord is severed the vein occasionally bleeds violently, but 'if, as is usual, the vein does not bleed at all, it can be identified as a large patulous vessel which contrasts with the two smaller, tightly contracted arteries' (Mollison, Mourant and Race, 1948). The catheter meets no resistance until it impinges upon the far wall of the left branch of the portal vein and it may even be introduced into the ductus venosus and so into the inferior vena cava.

Much information is available regarding the mode of anatomical obliteration of the intra-abdominal umbilical vein and the formation of the ligamentum teres hepatis (Robin, 1860; Wertheimer, 1886; Baumgarten, 1891; Butler, 1951). The account by Robin (1860) does not depict the relevant histological changes, so that interpretation of the obscure text becomes well-nigh impossible, and it is probable that sepsis was present in much of his young material. Wertheimer (1886) describes the formation of a central core of fibrous tissue completely filling the lumen of the vein. The obliterated lumen becomes surrounded by a musculo-elastic ring, while capillary formation in the central core of the fibrous tissue gives the spurious appearance of a tiny remnant of the original lumen of the vein. It is important to note that the youngest specimen described was from an infant aged 5 months. Baumgarten (1891) states that the lumen of the umbilical vein is not completely obliterated, and that a much reduced remnant, the *Rest-Kanal*, is to be found in most individuals. This opens into the left branch of the portal vein and extends for a varying distance along the ligamentum teres. Segall (1923) demonstrated this small vessel in 40% of injected adult human livers. In my opinion (Butler, 1951; 1952) the latter view is the correct one and is confirmed by the following observations, made on very young specimens. These observations also show why it is possible to use the intra-abdominal vein as a transfusion route in the early days of life.

MATERIAL AND METHODS

Thirty-one specimens of the intra-abdominal umbilical vein and ligamentum teres were examined; they ranged in age from birth to 77 years, but only

the 20 specimens between birth and 8 years are here considered in detail. Transverse sections were cut, in all specimens, at a point approximately midway between the umbilical ring and the left branch of the portal vein. In addition to routine haematoxylin and eosin staining, all sections were stained by the Weigert-van Gieson method for smooth muscle and elastic tissue.

The dimensions of certain sections were measured in the following manner. An image of the section, magnified 25 times (linear), was projected on to squared graph paper and its outline carefully delineated. The following areas were ascertained by counting the number of enclosed squares and converting the results into square millimetres:

A . . . Either (1) the cross-sectional area of the wall of the intra-abdominal umbilical vein, or (2) the cross-sectional area of the ligamentum teres
L . . . The cross-sectional area of the lumen of the intra-abdominal umbilical vein
l . . . The cross-sectional area of the residual lumen of the intra-abdominal umbilical vein found in the centre of the ligamentum teres
a . . . The area enclosed by the musculo-elastic ring, i.e., the area of the central core of new fibrous tissue

Assuming the vein to be of circular cross-section during life, an estimate of its internal diameter (D) was made. The thickness of the vein wall (T) was measured directly with an eyepiece micrometer. Owing to the manner in which the specimens had been removed after death, it was not possible to measure the length of the vein or the ligament.

OBSERVATIONS

Intra-abdominal Umbilical Vein between Birth and 13 Days

Dimensions. Table 1 lists the dimensions of nine of the 14 specimens included in this age group.

TABLE 1
DIMENSIONS OF SPECIMENS AGED 0 TO 13 DAYS

Number		Age	A (sq. mm.)	L (sq. mm.)	D (mm.)	T (mm.)
Type A	1	Full term	6·75	4·50	2·5	0·515
	5	45 minutes	7·72	3·77	2·2	0·700
	6	6 hours	3·22	3·92	2·3	0·220
Type B	3	Full term	8·65	1·41	1·4	0·825
	7	10 hours	5·77	0·61	0·9	0·880
	8	19 hours	7·12	0·65	0·9	0·810
	9	28¾ hours	5·32	0·88	1·1	1·045
	10	48 hours	4·71	1·34	1·3	0·750
	11	48 hours	4·73	0·60	0·9	0·750

The remaining five specimens, having been opened, could not be measured accurately, but their general appearances indicate that they fall into one or other of the two types. All specimens show a widely patent lumen and none shows any evidence of ante-mortem thrombosis. Type A specimens are characterized by a thin wall and a large lumen; type B specimens have a thicker wall and a proportionately smaller lumen. These proportions obtain whether the vessels be circular or oval in cross-section (Fig. 1). With the exception of specimen 3, the thin-walled veins are younger than the thick-walled.

Comparison of the average dimensions of the two types clearly indicates that considerable changes in size of lumen and wall-thickness are accompanied by a negligible change in the cross-sectional area of the vessel wall (Table 2). This indicates that the vein has undergone a partial contraction, reducing the average diameter of the lumen from 2·33 to 1·1 mm. If allowance be made for shrinkage due to fixation and dehydration it is clear that the lumen of the partially contracted intra-abdominal umbilical vein is of the same order of size as the polythene catheter used for exchange transfusion. The older specimens, aged 3½ to 13 days, were not measurable accurately, but the estimated dimensions of their lumina and walls are in keeping with those found for type B. No accurate indication of the time of occurrence of the partial contraction, in relation to the onset of respiration, can be gathered from the material available. All specimens older than 10 hours are in a state of partial contraction.

TABLE 2
AVERAGE DIMENSIONS

	Type A	Type B	Difference (%)
A	5·80 sq.mm.	6·05 sq.mm.	4 increase
L	4·16 sq.mm.	0·91 sq.mm.	78 increase
D	2·33 mm.	1·10 mm.	57 decrease
T	0·515 mm.	0·842 mm.	63 increase

Histological Appearances. The histological appearances of the two types of vein completely accord with the view that the dimensional changes are due to the contraction of the intramural smooth muscle.

Type A. The wall of the intra-abdominal part of the umbilical vein does not exhibit the classic picture of tunica intima, tunica media and tunica adventitia (Fig. 2, **1**; Fig. 3, **1**) and is best described as follows. Immediately beneath the endothelium is a narrow musculo-elastic zone containing a layer of longitudinal smooth muscle, one to two cells deep. Interspersed among the smooth muscle fibres is a longitudinal network of elastic fibres, forming a thin (occasionally incomplete) internal elastic layer. In section this layer

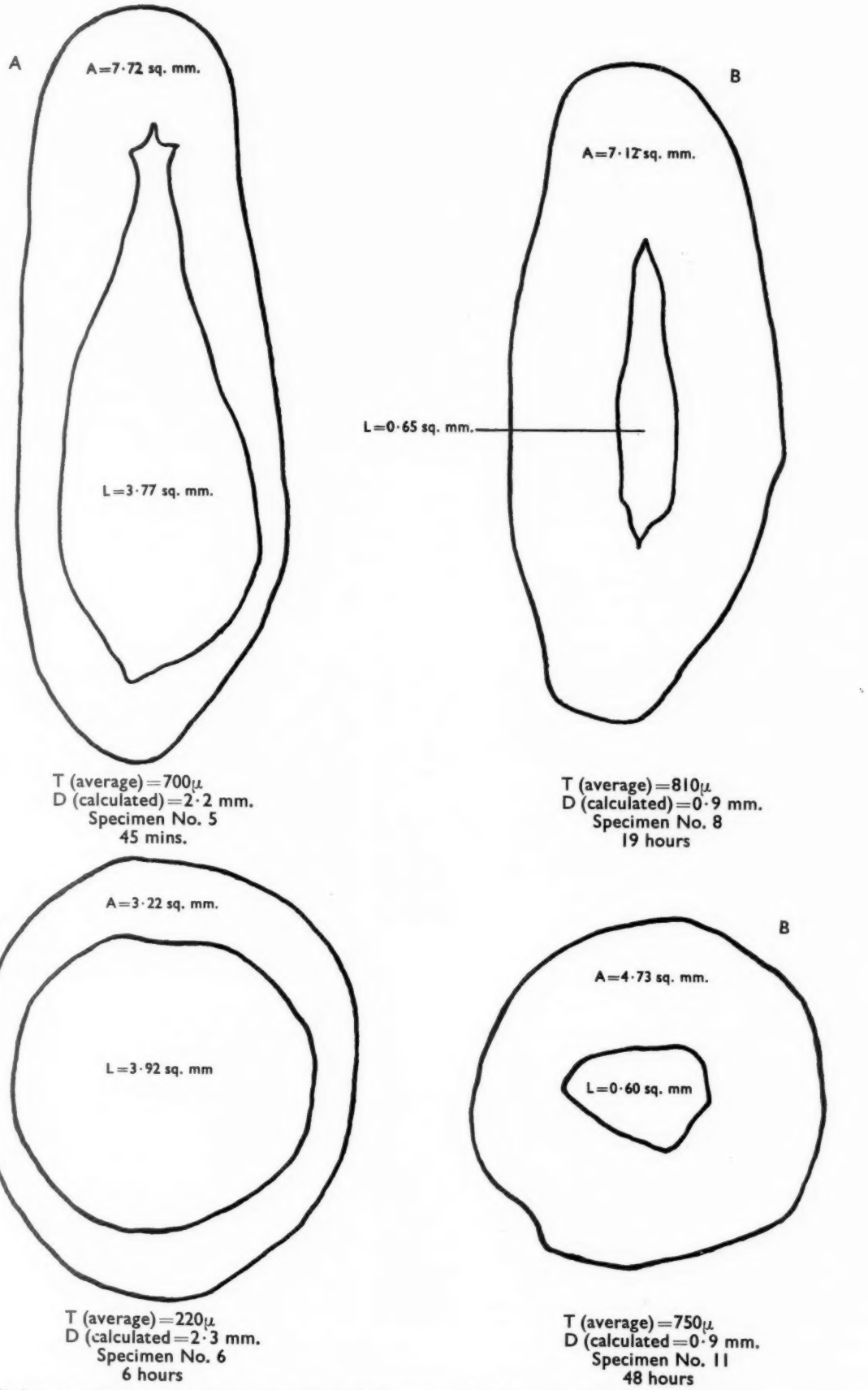


FIG. 1.—Tracings of sections of the intra-abdominal umbilical vein in the relaxed (type A) and contracted (type B) states. Examples of the circular and ovoid types are shown. All × 25.
Photomicrographs of specimens 6 and 11 are shown in Fig. 2 (1 and 2) and Fig. 3 (1 and 2).

FIG. 2.

1.—A segment of the wall of a type A (relaxed) vein showing the slender fasciculi of smooth muscle (M) widely separated by connective tissue. Specimen No. 6. Haematoxylin and eosin. × 13.

2.—A comparable segment of the wall of a type B (contracted) specimen showing the thickening of the fasciculi of smooth muscle (M), the increased density of the inter-muscular fibrous tissue and the prominent intima (I). Specimen No. 11. Haematoxylin and eosin. × 42.

3.—Transverse section of the extra-abdominal umbilical vein of a 6-month foetus showing the muscular structure (M) of its wall. Haematoxylin and eosin. × 13.

4.—Transverse section of a type B (contracted) vein showing a hillock of young connective tissue (H) obtruding into the lumen through a gap (E) in the dense internal elastic layer. Specimen No. 3. Weigert-van-Gieson stain. × 13.

appears as a row of black dots immediately adjacent to the endothelium. The main bulk of the vessel wall consists of white fibrous tissue containing fasciculi of smooth muscle fibres (Fig. 2, **1**), arranged in open spirals widely separated by white fibrous tissue. Intimately associated with the muscle fasiculi are long elastic fibres disposed parallel to the long axis of the muscle fibres. This main part of the vein wall forms a fibro-muscular media which, on its inner aspect, merges with the musculo-elastic zone. Externally the tunica media presents a clear-cut margin (Fig. 3, **1**) surrounded by fine, white connective tissue—the extra-peritoneal tissue of the falciform ligament. This contains numerous blood vessels and nerves and takes the place of a conventional tunica adventitia.

Type B. General features are similar to those of type A, but certain structures are rendered more prominent by the state of partial contraction. The spiral muscle fasciculi of the media are more obvious: they appear to run a more circular course and to be set closer together (Fig. 2, **2**; Fig. 3, 2). Individual muscle fibres are bulkier and shorter, and their appearance is unchanged at the thirteenth day after birth. The muscle content of the intra-abdominal umbilical vein is considerably less than that seen in the extra-abdominal umbilical vein of a six-months foetus (Fig. 2, **3**)

The musculo-elastic zone, particularly its elastic fibres, is more obvious since its components are now crowded within a much smaller perimeter. The elastic fibres appear as a zone of black dots, five or six deep, immediately next to the endothelium (Fig. 2, **4**; Fig. 3, **2**). This prominent musculo-elastic zone remains visible for almost the whole of life as an easily identifiable landmark, indicating the position of the inner surface of the partially contracted intra-abdominal umbilical vein. Further evidence of contraction is seen in the crenation of the inner margin of the vein and the close apposition of the nuclei of the endothelial cells. Where a gap occurs in the musculo-elastic zone a small hillock of young connective tissue projects into the vessel lumen (Fig. 2, **4**). The bases of these connective tissue hillocks extend outwards into the fibro-muscular media. The hillocks are the result of sub-intimal proliferation which begins before birth and the new tissue is, as it were, extruded into the lumen through the gaps in the musculo-elastic zone when the vessel contracts. Their appearance marks the beginning of the lengthy process of anatomical obliteration of the vessel lumen.

The intra-abdominal umbilical vein receives a number of small tributaries, namely its own vena venarum and the veins of Burow. The latter connect the epigastric venous plexus with the portal venous system via the intra-abdominal umbilical vein, and are relatively much larger in the foetus and neonatus than in the adult. They contain valves which direct the blood-flow towards the portal vein. It is therefore most probable that the blood found in the partially contracted intra-abdominal umbilical vein is an inflow from these tributaries and not a backflow from the portal vein.

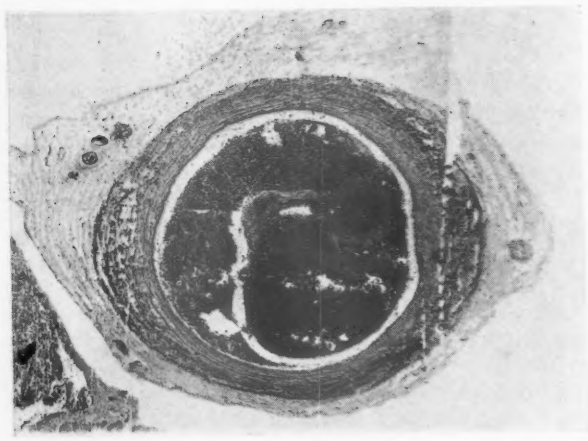
Formation of the Ligamentum Teres from 1 Month Onwards

The various stages in the formation of the ligamentum teres are seen in specimens aged from 1 month to 8 years. Three main and simultaneous processes seem to be involved in the further reduction of the lumen of the umbilical vein. These are as follows :—

Side-to-side Flattening of the Vein. This process, already present in the very young specimens, is most marked at 1 month (Fig. 2, **3**). In this specimen the lumen is reduced to a cleft about 3·0 mm. long with its long axis in the sagittal plane. The sides of the cleft are in contact for some two-thirds of its length and in some places the apposed walls are united by newly formed white fibrous tissue. The maximum diameter of the lumen is seen to be about 80 to 100 μ.

Formation of New Connective Tissue inside the Lumen. This is achieved by the continued growth of the hillocks protruding through the gaps in the musculo-elastic zone. This new tissue spreads irregularly around the lumen of the vein, always disposed between the endothelium and the musculo-elastic zone and thus forming the central core of the fibrous tissue first described by Wertheimer (1886). The patent lumen of the vein becomes greatly reduced but never completely obliterated (Fig. 3, **3**, **4**, **5** and **6**). At first the newly formed fibrous tissue consists solely of the white fibres but, from 8 years on, a few small and irregularly disposed elastic fibres are found. The bases of the hillocks, embedded in the fibro-muscular media, lay down much coarser collagen fibres and these eventually become indistinguishable from those which form the bulk of the ligamentum teres.

Composition of the Tunica Media. From 1 month onwards the smooth-muscle spiral fasciculi become distorted and disrupted by the increasing collagenous tissue composed of coarse collagen fibres. Interspersed among the collagen fibres are moderately



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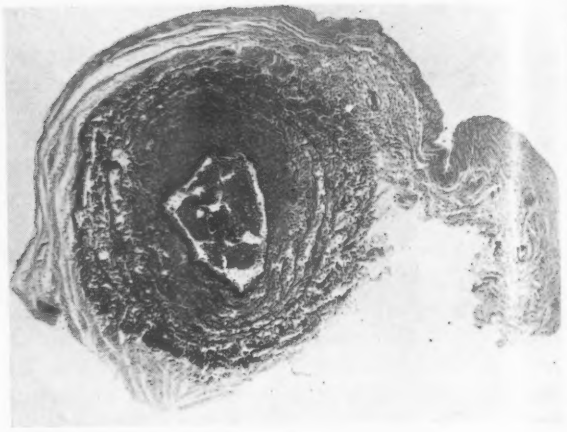

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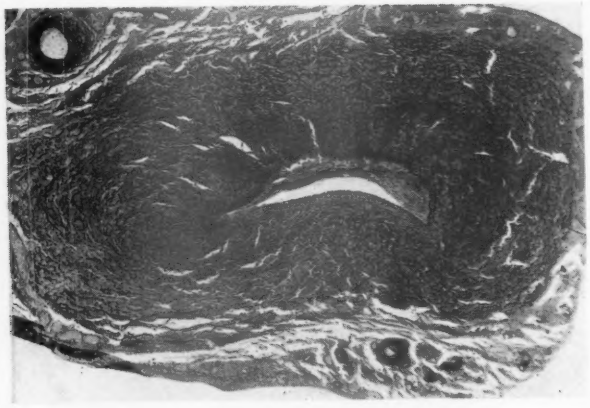

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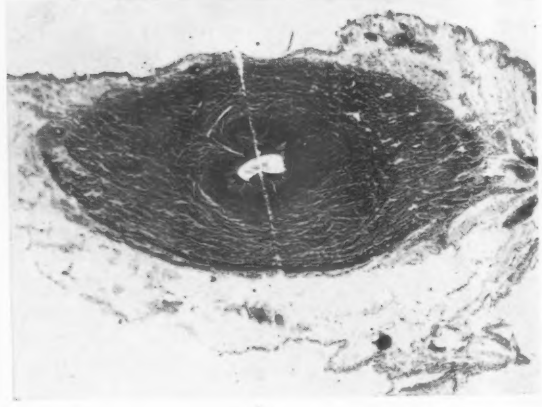

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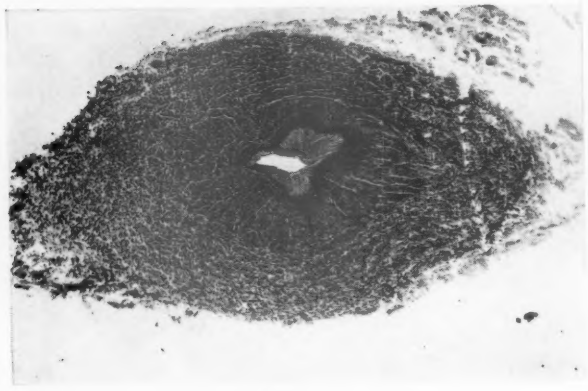

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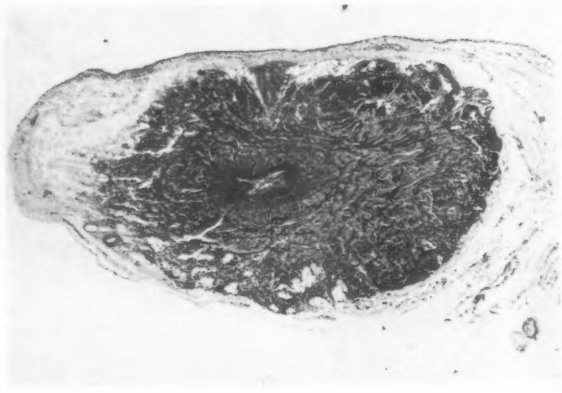

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FIG. 3.—Cross sections of the intra-abdominal umbilical vein and ligamentum teres from birth to 8 years. Weigert-van Gieson. All × 13.

1.—Type A (relaxed) vein, specimen No. 6, 45 minutes old, showing the slender, widely separated muscle fasciculi and the tenuous internal elastic layer.

2.—Type B (contracted) vein, specimen No. 11, 48 hours old, showing the thickening of the muscle fasciculi and the increased density and width of the internal elastic layer. The latter shows a gap at the upper aspect of the lumen associated with a small hillock of new tissue (cf. Fig. 2, 4).

3.—Ligamentum teres, specimen No. 16, 28 days old, showing side-to-side flattening of the lumen and the increased amount of new connective tissue. This latter has clearly spread inside the internal elastic layer.

4.—Ligamentum teres, specimen No. 15, 3 months old, the final zonal pattern is now clearly established (see Fig. 4) and, as a result of shrinkage, the musculo-elastic zone is crenated and covers a much reduced perimeter.

5.—Ligamentum teres, specimen No. 19, 13 months old, the histological pattern is exactly as in the previous specimen.

6.—Ligamentum teres, specimen No. 20, 8 years old, showing increased reduction in the residual lumen and further contraction of the musculo-elastic zone. The main fibrous zone of the ligament now contains more elastic tissue and fat deposits at its periphery.

large longitudinal elastic fibres whose numbers increase with age. Coincident with these changes the ligament becomes increasingly vascular, particularly at its periphery and, by 8 years, fat cells are seen among the marginal collagen fibres (Fig. 3, 6). As the white fibrous tissue of the ligamentum teres increases in bulk so the area enclosed by the musculo-elastic ring decreases.

Swelling of the spiral muscle fibres and alterations in their staining properties indicate the onset of degenerative changes. In the older specimens these muscle fibres become increasingly difficult to find and can often be located only by the presence of the persistent spiral elastic fibres surrounding each muscle fasciculus. Between 3 and 6 months numerous mononuclear phagocytes are to be found around the degenerating muscle fibres. A few poorly staining and obviously degenerate muscle fibres are seen in the 8-year-old specimen but after this age they are no longer detectable. From 20 years onwards small, widely-spaced fasciculi of longitudinal smooth muscle appear amongst the collagen fibres and have all the appearance of a new formation.

Measurements of the cross-sectional area of the intra-abdominal umbilical vein and of the ligamentum teres indicate that growth of the ligament begins during the first year of life and attains its maximum by about 18 years, thereafter remaining constant (Table 3).

TABLE 3
GROWTH OF THE LIGAMENTUM TERES

Age	A (sq.mm., average)
Birth, type A	5·80
Birth, type B	6·05
1 to 6 months	5·89
1 to 8 years	7·05
13 to 18 years	13·85
31 to 63 years	12·62

The musculo-elastic zone remains clearly visible into the sixth decade by reason of the persistence of its elastic fibres. From 3 months onwards these elastic fibres become packed into an ever-decreasing perimeter until, at about 20 years, they become mutually separated by the formation of a ring of longitudinal smooth muscle fibres. It is probable, but not certain, that the original muscle fibres of this zone disappear during the first eight years of life and that the ring of muscle seen from 20 years onwards is an entirely new formation. As the elastic fibres become more closely packed together they form a crenated ring and enclose a reduced area. This area (L) is, of course, the equivalent of the area of the lumen of the intra-abdominal umbilical vein and it reaches its maximum reduction by about 8 years of age (Table 4). In its centre, and separated from the musculo-elastic ring by the fibrous tissue core, is the patent remnant of the intra-abdominal vein (l). This lumen, also, undergoes progressive reduction in size and by 8 years it has a cross-sectional area of 0·005 sq.mm. This lumen is present in all the specimens examined, up to the sixth decade, and its area varies between 0·005 and 0·22 sq.mm. It is always maximal at the hepatic end of the ligamentum teres and shows a tendency to increase slightly with age. In portal venous obstruction it may become greatly enlarged, attaining a diameter even greater than that of the original intra-abdominal umbilical vein (Butler, 1952).

TABLE 4

	Age	L (sq.mm.)	l (sq.mm.)
Type A (average)	Birth	4·16	4·16
Type B (average)	Birth	0·91	0·91
Specimen No. 16	1 month	0·47	0·07
Specimen No. 15	3 months	0·25	0·06
Specimen No. 19	13 months	0·30	0·04
Specimen No. 20	8 years	0·08	0·005

By 3 months a cross section of the ligamentum teres shows the typical zonal arrangement (Fig. 4) recognizable up to the sixth or seventh decade of life, which is as follows:

Zone 1: A tiny central residual lumen of the intra-abdominal umbilical vein; occasionally doubled.

Zone 2: A zone of fine connective tissue formed by sub-intimal proliferation.

Zone 3: The elastic fibres of the original intima closely packed into an irregular ring. In later life a wide zone of longitudinal smooth muscle appears in the periphery of this ring.

Zone 4: The outer fibro-elastic zone, formed from the fibro-muscular media of the vein, and forming the bulk of the ligamentum teres. It contains, from 20 years onwards, a few longitudinal smooth muscle fibres and fat is laid down in its periphery.

The above sequence of changes is typical of sections taken at about the middle of the ligamentum teres or umbilical vein. At the hepatic extremity of the ligament the changes inside the elastic ring are modified by the absence or scant formation of new fibrous tissue. The residual lumen is therefore larger and is bounded by the musculo-elastic ring. At the umbilical extremity, however, the formation of the central core of fibrous tissue is more marked and all the residual lumen is completely obliterated. Furthermore, the fibro-elastic zone of the ligamentum teres forms a series of irregular tails

(Robin, 1860) which are connected to similar tails formed from the urachus and the obliterated intra-abdominal umbilical arteries. The material used in this present study did not permit investigation of the formation of these tails, which would appear, however, to be related to the growth in length of the ligamentum teres.

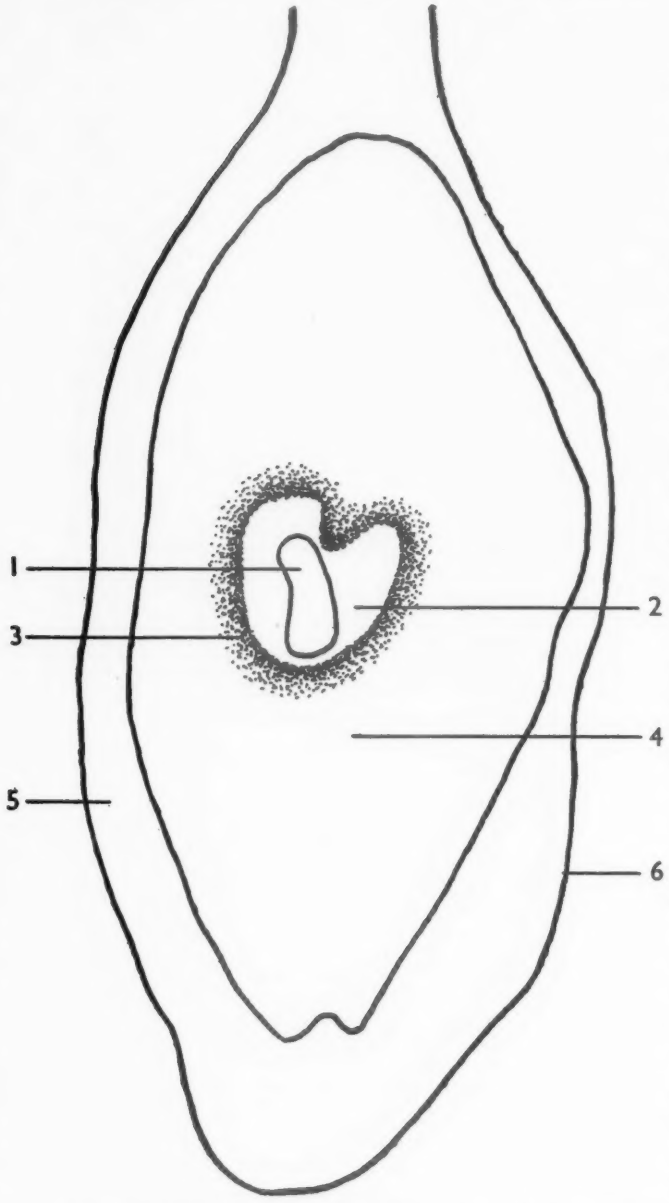

FIG. 4.—Tracing of a section of the ligamentum teres, aged 3 months, showing the typical zonal arrangement. (See Fig. 3, 4.) × 25.

1. Central residual lumen.
2. Connective tissue zone.
3. Musculo-elastic zone.
4. Fibro-elastic zone.
5. Extra-peritoneal tissue.
6. Peritoneum of the falciform ligament.

DISCUSSION

The dimensional and histological changes characterizing the intra-abdominal umbilical vein during the first 48 hours of life indicate that this vein has already partially contracted. Because of the scanty amount of smooth muscle in its wall the contraction is less complete than that which occurs in the umbilical arteries (Mollison *et al.*, 1948) or in the ductus arteriosus (Kennedy and Clark, 1941, Figs. 5 and 6). In these arterial vessels the lumen is almost completely obliterated so that the blood stops flowing. It is noteworthy that the intra-abdominal umbilical vein receives tributaries (the veins of Burow and its own vena venarum) which empty a small amount of blood into the vein after the cutting off of the placental inflow.

The average diameter of the lumen of the partially contracted vein, measured after fixation and sectioning, is 1·1 mm. This is in keeping with the ability to pass a polythene catheter of 1·0 mm. internal bore for the purpose of exchange transfusion. Further, a lumen of this order of size is found up to the thirteenth day after birth, so that the limiting factor in the utilization of this route for exchange transfusion is the formation of the umbilical scar and the falling off of the stump of the umbilical cord. The vein has, indeed, been utilized as late as the sixth day after birth (Diamond, 1954).

Anatomical obliteration of the lumen is well marked by the twenty-eighth day after birth but begins at, or just before, birth. Two main processes are apparent in such obliteration, viz., (*a*) a sub-intimal proliferation which fills the periphery of the lumen with new fibrous tissue, (*b*) the formation and subsequent contraction of coarse collagen fibres in the fibro-muscular media, such tissue forming the bulk of the completed ligamentum teres. These processes are further assisted by a side-to-side flattening of the partially contracted vein. There is no evidence to suggest that thrombosis and subsequent clot organization ever play any part in the normal process of obliteration. A marked gradient occurs in the intensity of obliterative change along the length of the vein, being maximal at the umbilical, and minimal towards the hepatic, end. This gradient appears to be related to the site of entry of the veins of Burow, which are so valved as to direct blood from the abdominal parietes towards the portal venous system. It is possible that this vascular connexion affords a route for the

haemal spread of cord sepsis into the liver of the newborn.

The evidence obtained from present material supports the view of Baumgarten (1891) that the lumen of the intra-abdominal umbilical vein is normally retained in the hepatic end of the ligamentum teres. It affords no support to the view of Wertheimer (1886) that the central lumen is caused by revascularization of the central fibrous-tissue core. The double or treble lumina which he regarded as diagnostic of new capillary formation are readily explicable by the irregular mode of growth of the tissue formed by sub-intimal proliferation.

SUMMARY

Soon after birth the intra-abdominal umbilical vein undergoes partial contraction and its lumen is reduced by about one-half.

Subsequent anatomical obliteration is incomplete and a tiny residuum of the original lumen persists at the hepatic end of the ligamentum teres.

Anatomical obliteration is a combination of (*a*) sub-intimal proliferation, (*b*) the formation and subsequent shrinkage of coarse collagen fibres in the fibro-muscular media, and (*c*) side-to-side flattening of the vein.

Thrombosis and subsequent clot-organization play no part in the obliterative process under normal conditions.

The elastic fibres of the venous intima persist, in the centre of the ligamentum teres, up to the sixth and seventh decades.

My thanks are due to Professor A. J. E. Cave for constant advice and encouragement. Particular gratitude is expressed to Dr. A. M. Barrett, Department of Pathology, University of Cambridge, and to his staff, for very generous and consistent supplies of material. To the departmental technicians, Miss J. Stedman and Mr. A. E. Westwood, are due respectively the sections and the photomicrographs.

REFERENCES

Barclay, A. E., Franklin, K. J. and Prichard, M. M. L. (1944). *The Foetal Circulation and Cardiovascular System, and the Changes that they Undergo at Birth*, pp. 74-75, 160-161, 219-220. Oxford.
Baumgarten, P. (1891). *Arb. path. Anat. Inst., Tubingen*, **1**, 1.
Butler, H. (1951). *J. Anat., Lond.*, **85**, 430.
—— (1952). *Thorax*, **7**, 159.
Diamond, L. K. (1947). *Proc. roy. Soc. Med.*, **40**, 546.
—— (1954). Personal communication.
Kennedy, J. A. and Clark, S. L. (1941). *Anat. Rec.*, **79**, 349.
Mollison, P. L., Mourant, A. E. and Race, R. R. (1948). *Med. res. Coun. Memo. No.* 19, pp. 43-45.
Robin, C. (1860). *Mém. Acad. Méd., Paris*, **24**, 391.
Scammon, R. E. and Norris, E. H. (1918). *Anat. Rec.*, **15**, 165.
Segall, H. N. (1923). *Surg. Gynec. Obstet.*, **37**, 152.
Sidbury, J. B. (1923). *Amer. J. Dis. Child.*, **25**, 290.
Wertheimer, E. (1886). *J. Anat., Paris*, **22**, 1.

THE USE OF THE INSULIN ZINC SUSPENSIONS IN DIABETIC CHILDREN

BY

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(RECEIVED FOR PUBLICATION MAY 10, 1954)

It is generally conceded that in children there is greater difficulty in achieving good control of diabetes with one daily insulin injection than there is in adults. At the same time it is in children especially that the need for fewer daily injections is felt.

The recent introduction of the new long-acting insulin zinc suspension (IZS) by Hallas-Møller (Hallas-Møller, Jersild, Petersen and Schlichtkrull, 1952) at the Novo Laboratories, Denmark, raised the two questions of whether this preparation could be used with success in children, and whether it offered advantages over the other long-acting insulins. The amorphous form of IZS (Novo 'semilente') is said to act for 12 to 16 hours after injection, and the crystalline form (Novo 'ultralente') for more than 24 hours. Novo 'lente' is a stable mixture containing 30% amorphous and 70% crystalline IZS. Reports on the use of IZS in adult diabetics have so far tended to be mainly favourable (FitzGerald, Thorn and Malins, 1954; Hallas-Møller *et al.*, 1952; Lawrence and Oakley, 1953; Murray and Wilson, 1953; Nabarro and Stowers, 1953; Venning, 1954). Lawrence (1954) states that children have responded well. When IZS (Novo) became available to us in August, 1953, we decided to conduct a trial in diabetic children. The first aim was to assess its practical value by clinical standards, regarding satisfactory clinical control as the most important criterion, and blood sugar studies primarily as an aid to achieving this. The standards for satisfactory clinical control were that the children should, while leading unrestricted lives, feel well and be free of all symptoms, with an upward weight trend. At the same time the urine should remain free of acetone, and a daily urinary sugar loss of not more than 10% of the daily carbohydrate intake was considered desirable. In this paper classification of clinical control has been restricted to two categories. Wherever control fell below the 'satisfactory' standard (as defined above), it has been classed as 'poor'.

A secondary aim of the study was to compare, by simple clinical and biochemical criteria, the control obtainable respectively with two daily injections of soluble insulin and one of insulin zinc suspension.

Methods

These studies were made at the Royal Hospital for Sick Children, Bristol (11 cases), and the Royal United Hospital, Bath (four cases).

The children were admitted to hospital but were allowed, so far as was possible, to lead lives of unrestricted activity, and regularly attended the physiotherapy department and handwork room. Each child was kept on a diet of constant calorie value, with approximately three parts of carbohydrate to one each of protein and fat. The total calorie content was based on the age of the child, after Collens and Boas (1946).

The main meals were given at 8 a.m., mid-day, 4 p.m., and 7.30 p.m. They were of roughly equal calorie value, except in the case of the smaller children who were given only milk and biscuits in bed at 7.30 p.m. All the children had a cup of milk at 10 a.m.

Urines were tested four-hourly for sugar and acetone by Benedict's and Rothera's methods. The total 24-hour urinary sugar output was measured three times weekly and on days when blood sugar studies were made. Insulin injections were given immediately before breakfast (8 a.m.) and at 7.30 p.m.

The following programme was adhered to whenever circumstances allowed. As a first step where necessary the 'old' cases were re-stabilized without changing the insulin preparation. When adequate control was established, capillary blood sugar levels were estimated over a 24- or 48-hour period by King and Garner's colorimetric method. Samples were taken at 8 a.m., 12 noon, 4 p.m., 7.30 p.m. and 11 p.m. or midnight. Treatment was then changed to a single injection of insulin zinc suspension, given at 8 a.m., starting with the same total number of units previously required each day. This dose was subsequently adjusted, as indicated by the results of urine testing. Usually some increase in total dose was necessary (*vide infra*). As soon as control again seemed satisfactory, 24- or 48-hour blood sugar studies were repeated. In most of the children a number of blood sugar studies were made with different doses and combinations of the Novo preparations of IZS.

TABLE 1
DETAILS OF 15 DIABETIC CHILDREN TREATED WITH IZS AND AN ASSESSMENT OF THE CONTROL ACHIEVED

	Case No.	Age	Sex	Duration of Diabetes	Estimate of Recent Control	Insulin Before Transfer a.m.	Insulin Before Transfer p.m.	Optimum Type and Dose of IZS	Duration of 'Follow-up'	Estimate of Control with IZS
Old Cases	1	7½	F	2 years	Satisfactory	SI. 25	SI. 18	Lente 50	5 months*	Satisfactory
	2	8	F	9 months	Satisfactory	SI. 28	SI. 21	Semilente 30 Lente 20	5 months	Satisfactory
	3	4½	F	6 months	Satisfactory	SI. 11 PZI. 5	SI. 12	Lente 30	5 months*	Satisfactory
	4	9½	M	2½ years	Poor	SI. 30	SI. 16 PZI. 4	Lente 60	4 months	Poor
	5	14½	M	2½ years	Poor	SI. 40 PZI. 15	SI. 20	Lente 100	5 months	Satisfactory
	6	15	F	10 years	Poor	SI. 40	SI. 40 PZI. 8	Lente 100	2½ months	Poor
	8	11½	M	9 months	Satisfactory	SI. 16	SI. 18	Semilente 10 Lente 24	5 months	Satisfactory
	9	6½	F	2½ years	Satisfactory	SI. 18	SI. 16	Lente 32	4 months	Satisfactory
	12	10	M	4 years	Satisfactory	SI. 32	SI. 26	Lente 72	5 months*	Satisfactory
	13	14	F	6 years	Poor	SI. 24	SI. 14	—	—	Poor
	14	6½	M	3½ years	Poor	SI. 8 PZI. 8	—	Lente 30	2 months	Satisfactory
New Cases	7	12	M	3 weeks	—	SI. 4	SI 4	Lente 4 Ultralente 4	6 months*	Satisfactory
	10	6	F	3 months	—	SI. 20	SI. 10	Lente 30 Ultralente 10	2 months	Satisfactory
	11	5	F	3 months	—	—	—	Lente 8 Ultralente 5	3 months	Satisfactory
	15	10	M	2 months	—	—	—	Lente 24	2 months	Satisfactory

* Indicates a change in dose in IZS since discharge from hospital, a reduction in all cases except No. 7.

No blood sugar studies were made until at least the third day after a change in insulin dosage. In four of the old cases re-stabilization was not complete before transfer to IZS, and two of the new cases were treated with IZS from the start. After discharge from hospital all the children were seen at first weekly until it was evident that control was being maintained.

Results

So far 15 children, between the ages of 4½ and 15, have been studied. Four of these, aged 5½, 6, 10 and 12, were new cases. Ten children have continued under observation as out-patients for periods exceeding three months, and four for two months.

In Table 1 are shown details of all the cases, and the results of our assessment of control by IZS in hospital and subsequently. The results in terms of total numbers are summarized in Table 2. It is convenient to consider the previously treated ('old') cases and the new untreated cases separately.

TABLE 2
ASSESSMENT OF CONTROL BY IZS IN HOSPITAL AND AT HOME

	Control by IZS					
	In Hospital			At Home		
	Total	Satisfactory	Poor	Total	Satisfactory	Poor
Old cases	11	10	1	10	8	2
New cases	4	4	0	4	4	0
All cases	15	14	1	14	12	2

Old Cases (Total 11). Ten of these were previously maintained on two daily injections of soluble insulin, four of them with the addition of a small amount of protamine-zinc insulin in the morning or evening.

One of the old cases (No. 14) had been previously maintained on a single morning injection of mixed soluble and protamine-zinc insulin. In 10 of the 11 children the clinical control obtained in hospital with one daily injection of IZS was judged to be satisfactory. In one child (Case 13) it proved impossible to maintain adequate stabilization in hospital with IZS even after a protracted trial.

Ten of the 11 old cases have been observed as out-patients, eight for periods between four and five months, and two for two months. Of the 10, eight have remained well stabilized and no major alterations in their insulin dosage or diet have been necessary.

In the following three children we failed to achieve or to maintain satisfactory control with IZS:

(1) A boy aged 10 (Case No. 4) was previously on soluble insulin, 30 units in the morning, and 16 units plus 4 units of PZI in the evening. Since developing

diabetes when aged 7, he had proved particularly unstable and he had often been re-admitted to hospital with bouts of vomiting and ketonuria. He seemed well stabilized in hospital on Novo 'lente', 60 units, but two months after discharge was re-admitted with vomiting and ketonuria. After 36 hours of treatment with soluble insulin eight-hourly he had recovered, and Novo 'lente' insulin was resumed at its former dosage. Again, control seemed satisfactory. However, since then he has had two similar relapses, both beginning at home.

(2) A girl aged 15 (Case No. 6) was previously on soluble insulin, 40 units b.d., with PZI, 8 units, in the evening. Since puberty she had been difficult to keep stabilized and her insulin requirement had been increasing. On some days glycosuria was very heavy, and on others she suffered from hypoglycaemic symptoms. In hospital Novo 'lente', 100 units, daily, appeared to be the optimum dose, and control seemed better. However, after 10 weeks of observation as an out-patient, she was admitted to the adult wards of another hospital with a severe hypoglycaemic attack, which had occurred in the forenoon. Soluble insulin has been resumed.

(3) It had recently proved difficult to maintain stabilization with soluble insulin in a girl aged 14 (Case No. 13). Glycosuria was heavy and difficult to control without risk of hypoglycaemic symptoms. Despite prolonged trial of varying doses and proportions of amorphous and crystalline IZS, satisfactory control could not be maintained for more than a few days at a time without further changes in dose. She was rather better stabilized when soluble insulin twice daily was resumed. For either form of insulin her new requirement lay between 50 and 60 units daily.

New Cases (Total Four). Two of these children (Cases 7 and 10) were first brought under control with soluble insulin before IZS was begun. Both were satisfactorily controlled by IZS. Case 7 required a threefold increase in dosage during the first weeks after discharge from hospital, but has remained stable since then.

The other two new cases (Nos. 11 and 15), were treated from the start with IZS, preliminary soluble insulin not being used. Case 2 was given 'semilente' once daily (10 units) for a few days before 'lente' was begun. Case 15 was started immediately on one daily injection of 'lente' (15 units). In both children the initial response was good and satisfactory control was finally achieved with higher doses.

It may be mentioned that in these new cases the usual rapid gain in weight and return of well-being occurred. The disappearance of acetonuria and reduction in glycosuria was just as rapid in the cases treated initially with IZS as it was in the other two.

The histories of two children are given here as fairly typical examples of cases that have done well on IZS.

A.R., a girl aged 5, Case No. 11, was admitted on November 13, 1953, with a history of thirst, frequency of micturition and loss of weight for three months. On examination she weighed 35 lb. and looked thin, and there was heavy acetonuria and glycosuria. A study of spontaneous blood sugar variations showed a morning (fasting) level of 85 mg. %, and levels between 240 and 340 mg. % during the rest of the day. The four-hourly Benedict's tests on the urine were almost constantly 'orange'. Values of 31 and 19 g. for 24-hour urinary sugar output were obtained before the administration of any insulin.

Treatment was then begun with single morning injections of Novo 'semilente' insulin, 10 units. A 1,700 calorie diet was given. Within three days urinary acetone disappeared and after six days urinary Benedict's tests assumed an almost constant pattern of green or blue by day and orange at midnight and at 4.0 a.m. Urinary sugar output fell to between 9 and 17 g. a day. A 24-hour blood sugar study showed values below 155 mg.% for eight hours after the injection of 'semilente' insulin, and 350 mg.% at midnight. With 'lente', 10 units, the urinary sugar pattern remained the same, but a blood sugar curve showed a more rapid rise by day. On 'lente', 15 units, the blood sugar pattern was similar to that obtained with 'semilente', 10 units, with a midnight level of 265 mg. %. A mixture of 'ultralente', 5 units, and 'lente', 8 units, gave daytime levels between 65 and 140 mg. %, and 200 mg. % at midnight. With all these varying doses she was free of ketosis and hypoglycaemic symptoms. She gained 5 lb. during her stay in hospital and was always very active.

She was allowed home on January 14, 1954, on Novo 'lente' insulin, 15 units daily in the morning. A month later the combination of 'lente' and 'ultralente' was resumed. She has remained well stabilized during the three months since she left hospital.

J.R., a girl aged 7½, Case No. 1, had been a diabetic since the age of 5. She was admitted for a trial of IZS on August 22, 1953, aged 7½, having been fairly well controlled for some time by soluble insulin, 15 units in the morning and 8 in the evening, and a diet giving about 1,700 calories. On examination she looked well, weighed 49 lb., and there were no abnormal physical findings apart from glycosuria, and induration at the sites of insulin injection. A 1,900 calorie diet was given. The previous dose of soluble insulin was found, under hospital conditions, to be inadequate, and it was raised to 25:18. After changing to Novo 'lente' insulin, a requirement of about 50 units was soon apparent. With 55 units hypoglycaemic attacks occurred between 4 and 5 a.m., low blood sugars were found at mid-day and 4 p.m., and the daily urinary sugar output ranged from 1·5 to 7 g. On 50 units she remained free of hypoglycaemic symptoms and from ketonuria, although her urinary sugar output was sometimes rather high. Repeated 24-hour blood sugar studies showed lowest levels sometime between mid-day and 8 p.m. and highest levels at midnight. The curves obtained with two daily injections of soluble insulin had shown a similar shape

FIG. 1.—A comparison in five children of daily blood sugar variations when stabilized on two injections of soluble insulin and on one of IZS. (In two cases protamine-zinc insulin accompanied one of the two soluble insulin injections as shown.)

and range. During one period she developed acetonuria and heavy glycosuria, probably as a result of injecting her insulin into sites of marked local induration. During the month after her discharge home on October 23 the dose of Novo 'lente' had to be progressively dropped from 50 to 40 units to avoid mild symptoms of hypoglycaemia in the late afternoon. On the latter dose she has remained very well stabilized for five months.

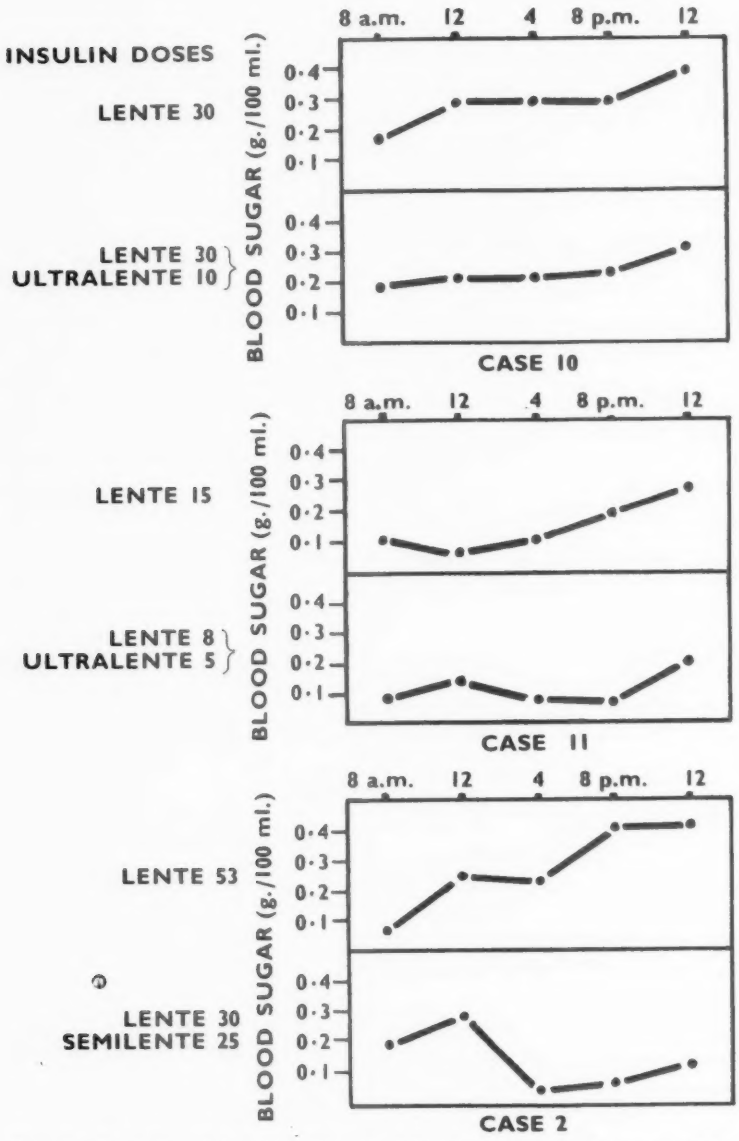

FIG. 2.—Examples of improved control of blood sugar obtained in three diabetic children by combining 'ultralente' (crystalline IZS) or 'semilente' (amorphous IZS) with IZS Novo 'lente.'

Discussion

During these studies the lability of diabetic children in terms of variations in urinary glucose loss and insulin requirement was often evident. Even when insulin dosage and calorie intake were kept constant, and in the absence of infection or of any known environmental change, considerable variations in the daily urinary sugar output occurred in individual children. Even in apparently stabilized children these variations in glycosuria were often of the order of $\pm 50\%$. Apart from day-to-day variations, there was often a more gradual swing towards increased or diminished glycosuria, and to different insulin requirements. In one case at least emotional factors appeared in some way to be operative.

These spontaneous variations could conceivably reflect changes in endogenous insulin production. The fact that two of our most unstable cases were girls at or near puberty may indicate the influence of changes in hormone balance on the insulin requirements of the body. Whatever the mechanisms of these changes, they produce, when insulin requirement is being studied, a 'shifting baseline', and make short-term comparisons of different insulin preparations difficult and liable to fallacious interpretation. Bearing this in mind, however, our experience so far has enabled us to reach certain broad conclusions concerning the use of insulin zinc suspension in children.

Blood Sugar Levels. As judged by the range of the daily blood sugar variations, it has been possible, in all the nine children who were well stabilized before transfer, to obtain as good control with one injection of IZS as with two of soluble insulin. The cases used for this comparison are shown in Table 3. In three of them a small proportion of protamine-zinc insulin accompanied one of the soluble insulin injections. It should be stated that for any given patient the number of blood sugar studies done with IZS usually exceeded those done with soluble insulin, so that the picture obtained of blood sugar control with soluble insulin was probably the less complete. In most of the children the pattern of blood sugar changes varied in detail

from day to day even with the same insulin dose, but for a given type of insulin a basic shape of curve tended to recur in each child. It was possible to modify this basic curve by varying the proportions of amorphous or crystalline insulin zinc suspension. In a small proportion of the children, those with the highest insulin requirements, the pattern of the blood sugar variation was inconstant, and these children proved the most difficult to stabilize. It would doubtless have been possible to alter the blood sugar patterns by variations in the dietary distribution of carbohydrate, but in these studies diets were kept constant to facilitate the comparison of insulin action.

Of the 14 children discharged from hospital on IZS, nine were on Novo 'lente' alone. In Fig. 1 examples are shown of satisfactory blood sugar control obtained with the 'lente' mixture, with, for comparison, blood sugar curves obtained in the same children by injections twice daily of soluble insulin, in some cases combined with protamine-zinc insulin.

In three of the children, although 'lente' insulin gave good blood sugar control from 8 a.m. to 8 p.m., rather high midnight levels occurred. The addition of a proportion of the pure crystalline suspension ('ultralente') gave more prolonged control (Fig. 2). In the light of this experience it is possible that some of our earlier cases, stabilized on 'lente' alone, might have benefited from the addition or substitution of a proportion of 'ultralente'. Two of our cases were stabilized on a mixture of 'lente' and 'semilente'. In one of these 'lente' alone had repeatedly failed to prevent a rather steeply rising blood sugar level throughout the day (Fig. 2).

We have found, as similarly reported by others, a tendency for our cases on IZS to require a slightly higher dosage of insulin than previously (FitzGerald *et al.*, 1954; Venning, 1954). Of nine patients who were well stabilized before transfer to IZS, six required an increase in total units for good control with IZS. The average increase was 15%. In two cases the total was unchanged, and in one it was slightly less (Table 3).

TABLE 3
COMPARISON IN NINE CHILDREN OF TOTAL INSULIN REQUIRED DAILY FOR STABILIZATION BEFORE AND AFTER TRANSFER TO IZS

Case No.	Units Needed Daily				
	Before Transfer to IZS			IZS	% Increase or Decrease
	SI	PZI	Total		
1	43	—	43	50	+16
2	49	—	49	50	+ 2
3	23	5	28	30	+ 7
4	46	4	50	60	+20
6	80	8	88	100	+14
7	8	—	8	8	—
8	34	—	34	34	—
9	34	—	34	32	− 6
10	30	—	30	40	+33

SI = soluble insulin. PZI = protamine-zinc insulin.

Clinical Control. It has been possible to achieve satisfactory control with one injection of IZS in the majority of our cases, and so far to maintain good stabilization with the children leading normal lives at home. In four of the children adjustments have been made in insulin dosage or diet since they left hospital. Such adjustments must always be necessary in diabetic children if really good control is to be maintained, and will be needed with any insulin preparation.

It is noteworthy that those three children in whom we failed to maintain satisfactory control with IZS had all previously proved particularly difficult and unstable cases. Further, we cannot yet say finally whether these children are better controlled by the older insulin preparations than by IZS.

Our experience so far with insulin-zinc suspension has given us the general impression that its action is reliable and smooth. We have experienced no alarming episodes during transfer from other insulins to IZS. Hypoglycaemic symptoms, if they occurred, tended to be regular and predictable with a gradual onset. With the Novo 'lente' mixture, hypoglycaemic symptoms were commonest between 10 a.m. and 6 p.m., and in only one case did they occur in the early hours of the morning.

In children with severe ketosis and vomiting, and where there is a threat of diabetic coma, we have used frequent injections of soluble insulin, and we believe that soluble insulin must retain its place in the treatment of such crises.

Practical Considerations. There has been no evidence of loss of potency in IZS (Novo) while we have been using it. Under the low power of the microscope the cuboidal insulin-zinc crystals contained in 'lente' and 'ultralente' are easily seen. The number of crystals per cubic millimetre in two vials of 'lente' were estimated, using a red cell counting chamber. The crystal counts in the new vials and in the same vials when nearly empty after use in the ward showed no significant variation.

We have found it important in practice to think of the three preparations 'semilente', 'lente' and 'ultralente', in terms of the two basic components, viz. amorphous (shorter-acting) and crystalline (longer-acting) insulin zinc suspensions. Failure to do this resulted in our administering to one case a larger proportion of the amorphous form than was intended when adding 'semilente' to 'lente'. The

graph recently published by Thorn (1954) has proved useful in this respect.

In none of our cases so far has a local inflammatory reaction occurred at the site of injection of IZS. The importance of varying the injection sites each day to ensure regular absorption was impressed on us by our experience with one case. While in hospital this child developed ketonuria for no apparent reason, until it was discovered that she was injecting all her 'lente' insulin into one of two indurated sites on her thighs. As soon as injections were given elsewhere, control was restored. It needs to be borne in mind that if insulin is given once daily smooth absorption is even more essential to the maintenance of control than it is when injections are more frequent.

Conclusions

From this short experience with a small number of cases it would be unjustifiable to draw anything but tentative conclusions. Nevertheless our findings have been encouraging enough for us to consider that insulin zinc suspension is likely to prove a reliable and effective long-acting insulin preparation. It appears probable that, by its use, reliable control could be maintained with a single daily injection in the majority of diabetic children.

Summary

A study has been made of insulin zinc suspension (IZS) in 15 diabetic children.

In 14 of the 15 children it proved possible to obtain satisfactory control in hospital with one daily injection of IZS. Fourteen of the children have been observed as out-patients, and 12 of them have remained well stabilized, though changes in the dosage have been needed in four of them.

In three of the children maintenance of control with IZS was poor, in one child while in hospital, and in two after returning home. All three had previously proved particularly unstable.

Four of the children were previously untreated and all of these were eventually well controlled by IZS. Two of them were treated initially with IZS and responded well.

In nine children blood sugar control with soluble insulin and with IZS was studied for comparison. The control obtainable with one daily injection of IZS was in all of them at least equal to that given by two injections of soluble insulin.

There has been no evidence of deterioration in the activity of IZS during the study, and no evident reactions have occurred at the sites of its injection.

It is suggested that the majority of diebetic children could probably be satisfactorily controlled by a single daily injection of insulin zinc suspension.

I wish to thank Professor A. V. Neale, Dr. John Apley and Dr. Beryl Corner for enabling me to carry out this clinical trial in children under their care, and for much help at all stages, including valuable criticism of this paper. Dr. G. K. McGowan kindly arranged special laboratory facilities for the Bristol cases, and Mr. H. Donaldson did the majority of the blood sugar estimations; I am much indebted to both of them. I am also indebted to Dr. Rachel Douglas who carried out much of the clinical work in the early stages. I am grateful to Dr. J. H. Smith for help with the cases at the Royal United Hospital, Bath, and to the staff of the Biochemical Laboratory there.

Evans Medical Supplies Ltd., supplied the 'Novo' insulins before they were available generally.

References

Collens, W. S. and Boas, L. C. (1946). *The Modern Treatment of Diabetes Mellitus*. Springfield, Ill.
FitzGerald, M. G., Thorn, P. A. and Malins, J. M. (1954). *Lancet*, 1, 187.
Hallas-Møller, K., Jersild, M., Petersen, K. and Schlichtkrull, J. (1952). *J. Amer. med. Ass.*, 150, 1667.
Lawrence, R. D. (1954). *Brit. med. J.*, 1, 58.
—— and Oakley, W. (1953). *Brit. med. J.*, 1, 242.
Murray, I. and Wilson, R. B. (1953). *Ibid.*, 2, 1023.
Nabarro, J. D. N. and Stowers, J. M. (1953). *Ibid.*, 2, 1027.
Thorn, P. A. (1954). *Lancet*, 1, 190.
Venning, G. R. (1954). *Ibid.*, 1, 480.

RENAL AND VASCULAR DISTURBANCES IN A CASE OF THALLIUM POISONING

BY

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(RECEIVED FOR PUBLICATION MAY 5, 1954)

The following case report of thallium poisoning is of interest from several points of view. It emphasizes the effect of thallium on the renal and vascular systems and its role as a possible cause of hypertension even in childhood; it indicates that a complete cure may be obtained without the use of dimercaprol (B.A.L.); and it affords scope for discussion of the possible mechanisms whereby, in thallium poisoning, changes are produced in the kidneys and blood vessels.

Case Report

N.S., a 9-year-old Yemenite Jewish boy, five years in Israel, was admitted on May 2, 1953, from a boarding school because of slight neck stiffness. One week before admission the child had begun to limp and his behaviour became strange. Two days before admission he had complained of pains in the left leg, and on the following day he had refused to eat, vomited, lay curled up in bed, and had shown no interest in his surroundings. The temperature had been normal.

On admission to the Rambam Hospital the patient gave the impression of being seriously ill. He weighed 20·5 kg. and his temperature was 37° C. His build was slim and the nutritional state was only fair. He was apathetic, lay in bed with his body in flexion, and consciousnesswas clouded. The pulse was 104 and regular. The liver edge was palpable just below the costal margin. Slight neck stiffness was present. He held the left lower limb in a state of flexion, and the left thigh was tender to pressure. The plantar response on the left side was indefinite but occasionally extensor. The tendon reflexes were present and his gait was unsteady, almost waddling.

Lumbar puncture on admission yielded a clear fluid, not under pressure, and the cerebrospinal fluid showed an absence of cells and a negative Pandy reaction. Ophthalmoscopic examination of the fundi showed the discs to be normal. They remained so throughout subsequent examinations. Slit lamp examination of the anterior eye revealed no abnormality.

The child remained in this apathetic state for a number of days, was uncooperative, refused food and appeared very depressed. At night he complained of pain in the muscles of the left thigh. His gait remained unsteady, and there was a marked lumbar lordosis with prominence of the abdomen. On May 10 it was first noticed that the hairs of the scalp began to fall out in large amounts, the eyebrows remaining comparatively unaffected. The skin of the extensor surfaces of both hands showed a scaly, cracked and roughened appearance. The gums were red and swollen and they bled easily. On the following day similar skin changes were noticed over the ankles and on the forehead.

On May 11 there was a noticeable improvement in the child's general condition. He became cooperative and was much happier. About this time the possibility of thallium poisoning was considered. A detailed enquiry into the child's previous history revealed that he had always been well, happy and sociable. We learnt that thallium-coated wheat grain was used as a rat poison at the school, although special precautions were taken to prevent children having access to it. Furthermore, the child at first denied having eaten any such grain, though he later admitted to tasting it. Spectroscopic examination of the urine on May 15 revealed appreciable amounts of thallium, thus confirming absolutely the diagnosis of thallium poisoning. Spectroscopic examination of the blood on May 18 was negative for thallium.

On May 13 the blood pressure was first recorded and was found to be 170/145 mm. Hg, although the child's sole complaint was occasional pain in the left thigh. On the following day the blood pressure rose to 180/165 mm. Hg, and a second lumbar puncture yielded clear fluid under a pressure of 160 mm. water. The Queckenstedt test was positive, and cell and biochemical findings were normal. On May 15 the child suffered from two attacks of convulsions, separated by an interval of three hours. In the first attack he lost consciousness, maintained the left upper and lower limbs in flexion, and the limbs on the right side in extension. This was followed by clonic spasms, particularly on the left side. He became pale but did not foam at the mouth or pass urine. The convulsion passed after about two minutes, and the child immediately appeared to regain full consciousness. The second fit was accompanied by a short cry, and affected both sides of the body although more the left side. There were numerous small movements of the fingers of the left hand, but the child rapidly regained consciousness after the convulsion.

His general condition remained quite good, and he showed normal interest in his surroundings. The skin changes became progressively less marked. A detailed neurological examination showed sensation to light touch to be normal and the left plantar response to be extensor.

The blood pressure remained in the neighbourhood of 185/150 mm. Hg. Although the child did not show polydipsia, the specific gravity of the urine was 1,010 or less. The urine concentration and urea clearance tests showed definitely pathological values, as described below and shown on Fig. 1.

On May 24 he had a further attack of convulsions, which affected mainly the left side of the body and which passed without sequelae after five minutes. During the three days following this third fit the systolic blood pressure reached 200 mm. Hg. Frequent blood pressure measurements during the subsequent three weeks showed raised values with slight variations, but never falling below 140/100 mm. Hg with the patient in a recumbent position.

On May 28 a strict rice and fruit diet was instituted for 22 days. As there was no marked fall in blood pressure during this regime, trials with hexamethonium bromide were begun and the patient received three injections of this drug. Details of the response are given in the table. No B.A.L. was administered. About June 16 the blood pressure began to show a gradual but marked fall, and by June 20 a value of 115/75 mm. Hg was recorded. Accordingly the trial with hexamethonium bromide was not continued. The blood pressure did not tend to rise again and on July 11 it reached a constant value of 106/65 mm. Hg.

There was a steady improvement in the general condition, and the skin gradually returned to a normal state. From June 24 it was noticed that the scalp hair had begun to grow again. The inflammation of the gums regressed and the gingival mucosa regained a normal appearance.

The child early became alert and happy, had a good appetite and appeared well, both physically and mentally, even during the period of hypertension. The temperature never rose above 37·5° C. There was a steady improvement in the results of the urine concentration and urea clearance tests, which closely paralleled the return of the blood pressure to normal. These two tests of renal function were normal on discharge. On leaving the hospital on July 16, 1953, his general state was very good, and he had gained 500 g. in weight during his in-patient stay.

On June 15 there was a marked narrowing of practically all the retinal arteries, the arterio-venous ratio in many places being 1 to 3 instead of the usual 2 to 3. No haemorrhages or exudates were present. The disc, as already noted, was normal. The left fundus showed a similar appearance. It is not possible to state when the arteries became narrowed. This abnormal narrowing of the retinal arteries remained, although in a slightly less marked degree until the last fundal examination, which took place on October 4, 1953. On that date, in addition to the narrowing of the arteries, an increase in the central light streak of the arteries was noted. The latter fact and the continued narrowing of the arteries suggest that what may have been a functional condition had now been followed by organic changes. The visual acuities and visual fields were normal.

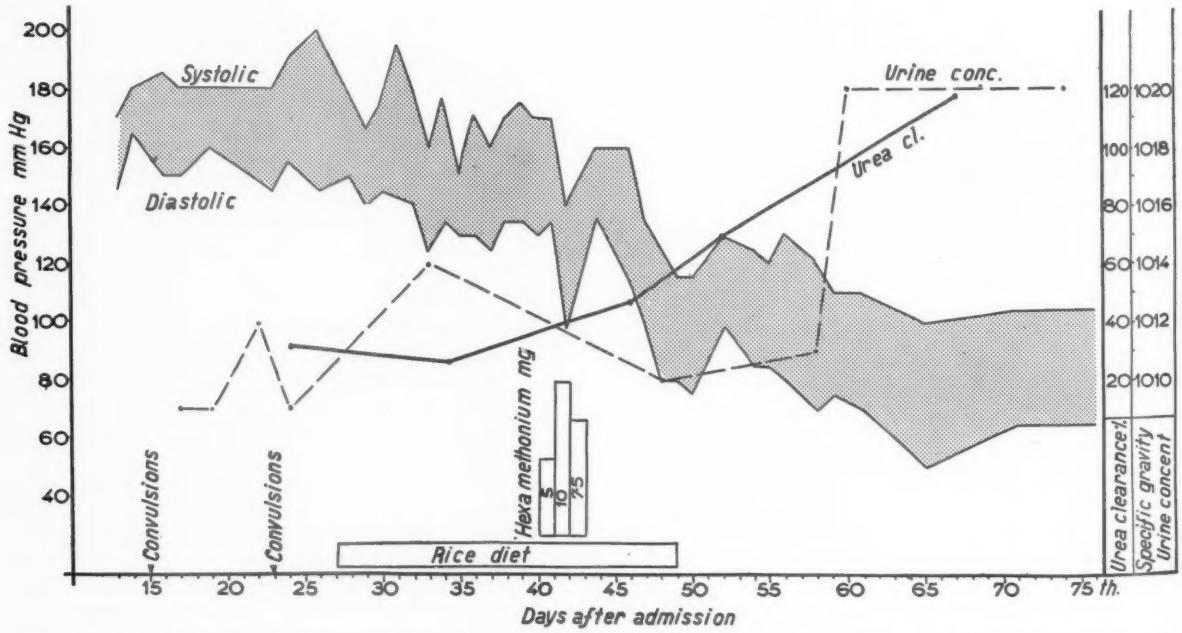

FIG. 1.—Correlation between blood-pressure changes and the results of kidney function tests, showing also the onset of convulsions and therapeutic measures.

INVESTIGATIONS. Laboratory investigations gave the following results:

Urine. May 3, albumin 0·5 0/00; May 6, trace of albumin leucocytes 1-3; cylindroids; May 12, no abnormal constituents; May 25 and June 1, trace of albumin; June 10 and further examinations, no abnormal constituents.

Urine Concentration Tests (*Specific Gravity*). May 18, 1009; May 23, 1012; May 25, 1009; June 3, 1014; June 18, 1010; June 28, 1011; June 30, 1016; July 5, 1020; three further examinations, 1020.

Urea Clearance Tests. These are expressed as a percentage of clearance for two hourly specimens. May 25, I: max. cl. 32%, II: max. cl. 30%; June 4, I: max. cl. 27%, II: stand. cl. 25%; June 16, I: max. cl. 47%; II: max. cl. 45%; June 22, I:max. cl. 70%; II: max. cl. 74%; June 29, II: stand. cl. 90%; July 7, I: max. cl. 118%, II: max. cl. 100%.

Blood Urea. Values between 16 and 25 mg. per 100 ml. were found.

TABLE
EFFECT OF SUBCUTANEOUS INJECTIONS OF HEXAMETHONIUM BROMIDE ON BLOOD PRESSURE

	Blood Pressure (mm. Hg)		
	Recumbent	Sitting	Standing
June 10			
Before injection	170/130		
Following 5 mg. dose			
30 min. ..	150/125	130/110	100/80
60 min. ..	130/115	130/110	120/105
3 hours ..	170/130	160/130	145/125
June 11			
Before injection ..	170/135	170/140	170/145
Following 10 mg. dose			
30 min. ..	90/0	85/0	
60 min. ..	108/80		
3 hours ..	128/100	120/100	130/110
June 12			
Before injection	140/100	145/100	140/130
Following 7½ mg. dose			
30 min. ..	105/80	100/80	
60 min. ..	110/85	120/100	105/70
3 hours ..	130/80		

Blood. Total proteins, 7·6 g. per 100 ml. (albumin 4·3/globulin 3·3); Weltman, 7; Takata Ara test negative; syphilis flocculation reaction negative; bilirubin test negative; cholesterol, 190 mg. %; alkaline phosphatase, 2·4 B.U. %; sugar, 88 mg. %; NaCl, 615 mg. %; potassium, 14 mg. %; phosphorus, 4 mg. %; prothrombin time, 100%; B.S.R. (Westergren), 35/65 on May 2, 28/53 on July 8.

Blood Counts. May 2, Hb. 13·5 g. per 100 ml; R.B.C., 4·5 m. per c.mm.; W.B.C., 4,300 per c.mm. (polymorphs 23%, basophil 1%, lymphocytes 73%, monocytes 4%); July 8, Hb. 10·4 g. per 100 ml.; R.B.C., 3m. per c.mm.; W.B.C., 5,000 per c.mm. (polymorphs 23%, basophil 1%, eosinophils 4%, lymphocytes 69%, monocytes 3%).

Radiographs. The chest, skull and left femur were normal. An electrocardiogram was within normal limits. The injection of 5 mg. benzodioxane on May 21 was not followed by a fall in blood pressure.

Discussion

This patient presented the usual features of acute thallium poisoning, e.g. alopecia, skin changes, gingivitis, behaviour changes, convulsions and polyneuritic pains. The diagnosis was confirmed by finding thallium on spectroscopic examination of the urine.

A raised blood pressure is a recognized finding in acute thallium intoxication (Munch, Ginsburg and Nixon, 1933; Mazzei and Schaposnik, 1949; Meyler, 1952; von Oettingen, 1952), although the literature pays scant attention to its possible aetiology. The paucity of studies on the causation of hypertension in thallium poisoning compels us to attempt to compare thallium intoxication with that due to lead, another heavy metal, with regard to blood pressure and renal disturbances.

Both Fishberg (1934) and Cantarow and Trumper (1944) have discussed fully the problem of early hypertension in lead poisoning. They conclude, on the basis of surveys of clinical experiences and experimental studies on animals, that this 'early' rise in blood pressure is definitely not of renal origin, but is due to the direct action of lead in causing contracture of the smooth muscle of the small blood vessels including capillaries. It is probable that the retinal vascular changes, as well as the transient nature of the hypertension in our case, is supportive evidence of a similar mechanism, i.e. peripheral arterioconstriction, being the cause of a raised blood pressure in thallium poisoning.

The transient nature of the hypertension indicates that the general vascular changes were functional in origin, while the continued narrowing of the retinal arteries suggests in one tissue at least that this functional disturbance may be followed by organic change.

The possibility of the hypertension being secondary to changes in the kidney is difficult to accept in our case, as hypertension secondary to acute kidney disease usually accompanies glomerulonephritis (Wright, 1952). Our patient did not show the picture of acute nephritis.

Another possible mechanism for the hypertension might be damage to the medullary vasomotor centre, a suggestion based on the necropsy findings of 'profound extensive changes' with nerve cell degeneration at the base of the brain, as well as on symptoms related to the nervous system (Munch *et al.*, 1933; Schild and Schrader, 1952). No signs of bulbar involvement were seen in our patient to confirm the possibility of damage to the vasomotor centre.

In considering whether the convulsions were due to metal poisoning of the cortical nerve cells or to

vasoconstriction alone, the fact that the convulsions in our case were limited to three short fits only, despite a prolonged period of hypertension, and the absence of papilloedema, are against a hypertensive origin of the fits.

Clinical reports on thallium poisoning show a high percentage of patients with urinary findings of albumin, red and white cells, and casts (Gleich, 1931; Ginsburg and Nixon, 1932; Munch, 1934; Kallner, 1946; Diengott, 1951; Grulee and Clark, 1951). Post-mortem examinations of the kidneys after thallium intoxication have shown marked hyperaemia, cloudy swelling and degenerative changes in the cells of the glomeruli and tubules (Lynch and Scovell, 1930; Rambar, 1932; Munch *et al.*, 1933).

The problem postulated by our case is whether the renal dysfunction was mainly the result of vascular spasm in the kidney, of direct toxic damage to the kidney cells, or of a combination of both factors. Albumin and cells in the patient's urine suggested glomerular damage, the reduced concentrating power of the kidneys suggested tubular dysfunction, and the clearance tests suggested damage to both glomeruli and tubules. The reversibility of the renal dysfunction, as judged by the various tests performed, indicated that the damage to the kidneys was not severe. There was a direct correlation between the fall in blood pressure and the recovery of normal kidney function, illustrated in Fig. 1. These clinical and laboratory findings suggest that the major factor in producing the renal dysfunction was the transient vasoconstriction within the kidney.

Hexamethonium bromide caused a marked depression of the blood pressure, the degree of the fall depending on the dose used. This fall in blood pressure in our patient offers no indication as to the cause of the hypertension in thallium poisoning, as the action of hexamethonium bromide on blood pressure is independent of the aetiology of the hypertension, whether renal or peripheral in origin (Lyons and Love, 1952). In our case the symptoms attributable to the raised blood pressure were indefinite. There is probably no indication to use this drug regularly unless the clinical picture shows severe manifestations of hypertensive origin. However, its use must be considered in cases of thallium poisoning, and a decision made on the individual patient.

A rice diet was given for 22 days, and during this time there was a slow downward trend in the blood pressure readings. However, one cannot conclude that this fall was due definitely to the effect of the diet alone, since the possibility of gradual detoxication by excretion of the metal cannot be excluded.

Experimental work on the use of B.A.L. in induced poisoning in animals has shown no clear benefit from the drug in this condition (Longcope and Luetscher, 1949). Although some authors have claimed good results from B.A.L. therapy in thallium poisoning (Mazzei and Schaposnik, 1949; Welty and Berrey, 1950; Diengott, 1951; Schild and Schrader, 1952), their reports cannot be judged as convincing evidence, particularly as improvement in this complex clinical picture is not easy to assess. Previous experiences in this hospital with three children after thallium poisoning treated with B.A.L. were not convincing of its value. For these reasons B.A.L. therapy was deferred, and the child in the meantime showed a spontaneous improvement leading to complete recovery without this drug. These experiences have left us unconvinced of the value of B.A.L. in thallium poisoning. It is noteworthy that the general opinion (Longcope and Luetscher, 1949) is that B.A.L. is not effective in lead poisoning.

Summary

A boy aged 9 years, suffering from thallium poisoning, showed marked hypertension, renal dysfunction and retinal vasoconstriction, as well as the more usual clinical features of this intoxication.

All the manifestations, with the exception of retinal vascular constriction, cleared without the use of B.A.L. (dimercaprol). Trial doses of hexamethonium bromide produced a marked temporary fall of the blood pressure.

The aetiology of the hypertension and renal damage is discussed, and the analogy with lead poisoning is drawn. It is considered likely that the thallium brings about hypertension by a direct action on the blood vessels.

We wish to thank Dr. W. Falk and Dr. N. Herz for their great interest and assistance. Dr. O. Schnapp, of the Israel Institute of Technology, kindly performed the spectroscopic examinations.

References

Cantarow, A. and Trumper, M. (1944). *Lead Poisoning*. Baltimore.
Diengott, D. (1951). *Acta med. orient., Tel-Aviv.*, **10**, 17.
Fishberg, A. M. (1934). *Hypertension and Nephritis*, 3rd ed. Philadelphia.
Ginsburg, H. M. and Nixon, C. E. (1932). *J. Amer. med. Ass.*, **98**, 1076.
Gleich, M. (1931). *Ibid.*, **97**, 851.
Grulee, C. G. and Clark, E. H. (1951). *Amer. J. Dis. Child.*, **81**, 47.
Kallner, A. (1946). *Ann. paediat., Basel*, **167**, 188.
Longcope, W. T. and Luetscher, J. A. (1949). *Advanc. intern. Med.*, **3**, 39.
Lynch, G. R. and Scovell, J. M. S. (1930). *Lancet*, **2**, 1340.
Lyons, R. H. and Love, V. L. (1952). *Advanc. intern. Med.*, **5**, 303.
Mazzei, E. S. and Schaposnik, F. (1949). *Brit. med. J.*, **2**, 791.
Meyler, L. (1952). *Side Effects of Drugs*, p. 84. Amsterdam.
Munch, J. C. (1934). *J. Amer. med. Ass.*, **102**, 1929.
——, Ginsburg, H. M. and Nixon, C. E. (1933). *Ibid.*, **100**, 1315.
Oettingen W. F. von. (1952). *Poisoning*, p. 484. New York.
Rambar, A. C. (1932). *J. Amer. med. Ass.*, **98**, 1372.
Schild, W. and Schrader, A. (1952). *Nervenarzt*, **23**, 288.
Welty, J. A. and Berrey, B. H. (1950). *J. Pediat.*, **37**, 756.
Wright, S. (1952). *Applied Physiology*, 9th ed., p. 357. London.

ENDOCARDIAL FIBRO-ELASTOSIS IN IDENTICAL TWINS

BY

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(RECEIVED FOR PUBLICATION MAY 3, 1954)

Fibro-elastosis of the endocardium in siblings has been reported on only two occasions, first by Ullrich (1938), who described it in two monovular offspring of male triplets, and secondly by Weinberg and Himelfarb (1943), who described it in two siblings. A further unrecorded example in siblings has also been mentioned to the authors (Bonham Carter, 1954). The condition in identical female twins therefore seems worthy of record.

Case Reports

J.C. and E.C. were identical female twins, blood group O, Rh positive, born normally at home on July 30, 1953. The parents were healthy, the mother aged 25 years and the father aged 28 years. There was one other healthy girl born one year before. The twins were admitted at the age of 18 hours because of poor housing conditions. Birth weights were: J.C., 4 lb. 8 oz. and E.C., 4 lb. 12 oz. No abnormality could be found in either on examination. They thrived satisfactorily. J.C. weighed 5 lb. 1 oz. when discharged at the age of 4 weeks on August 28 and E.C. 5 lb. 9 oz. on discharge on September 14 at 6½ weeks. At no time during this admission was any cardiac anomaly suspected or detected. The babies were seen at out-patients at the age of 12 weeks and were thriving well.

Case 1. J.C. was re-admitted on December 9, 1953, aged 19 weeks, with a history of vomiting feeds for one week following an upper respiratory infection with a running nose and cough. Difficulty in respiration, increased sweating and cyanosis around the mouth had been noticed. On examination the baby was pale and dyspnoeic, with a running nose. The temperature was 100° F. and the pulse 180 per minute, regular. The apex beat could not be located, the heart sounds were muffled but no murmurs were heard. The liver was enlarged three fingerbreadths below the costal margin and there was some rib recession but no sign of pneumonia or oedema. A diagnosis of cardiac failure of uncertain causation was made and the baby was put in an oxygen tent and given digoxin, 0·1 mg. intravenously, and then 0·1 mg. every eight hours orally for 24 hours, followed by 0·1 mg. b.d. for five days. Considerable improvement resulted.

Blood examination showed: R.B.C. 4·5 m. per c.mm., Hb 76% (11·2 g. per 100 ml.), colour index 0·9, W.B.C. 6,300 per c.mm., with a normal differential count. An electrocardiogram showed the heart to be in an indeterminate position with no special ventricular preponderance.

The baby began to improve and was discharged on December 24, 15 days after admission. She was feeding well, and the weight had risen to 10 lb. 8 oz. Ten days later, on January 3, 1954, she had to be re-admitted on account of the recurrence of cardiac failure; temporary relief from digoxin was obtained but she failed to gain weight and refused some of her feeds. Respirations were always rapid and cyanosis frequent. Radiographs of the chest showed a very large globular heart and a barium swallow showed the oesophagus to be displaced posteriorly and to the right due to enlargement of the left atrium.

On February 3, 31 days after her last admission, the baby died in heart failure.

NECROPSY.—The only striking abnormalities were those in the chest. There was a little serous fluid in

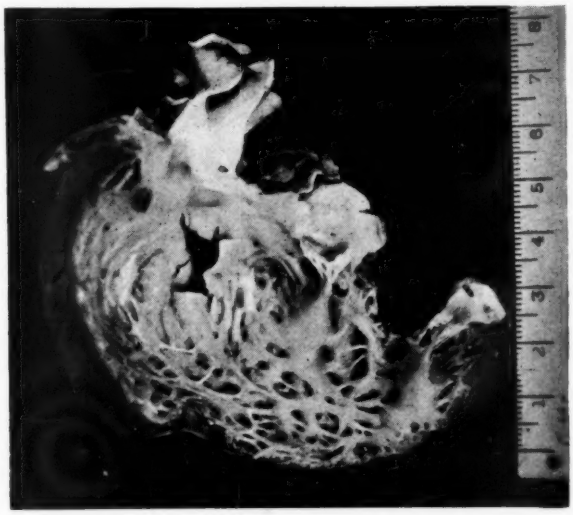

FIG. 1.—Case 1: left side of the heart showing white thickened endocardium and dilated chambers.

FIG. 2.—Case 1: right ventricle showing relatively normal appearance of endocardium.

each pleural sac and also in the pericardial sac. Both lungs were congested and there was a small area of bronchopneumonia at the apex of the right lung. The heart was enlarged and globular (maximum length 5·8 cm., maximum width 5·5 cm.) and weighed 52 g. (normal is 31 g., Coppoletta and Wolbach, 1933). The left ventricle (Fig. 1) was markedly dilated and hypertrophied. The thickness of its wall was 9 mm. and the right ventricle was hypertrophied but not obviously dilated (Fig. 2). Its wall thickness was 3 mm. The foramen ovale and ductus arteriosus were closed and there was no abnormality of the valves. The endocardium of the left side of the heart, both auricle and ventricle, was white and thickened.

HISTOLOGY. Sections of left ventricular muscle and of kidney, liver and spleen were stained for increased glycogen or fat with negative result. The heart muscle fibres were normal and there was no cellular infiltration. The elastin stains revealed a great increase in the number of elastic fibres in the thickened endocardium of the left ventricle, the elastic fibres being short and fragmented (Fig. 3). This appearance was even more striking in the endocardium of the left auricle (Fig. 4). There was also a patchy thickening of the endocardium with increase in elastic tissue in a section taken from the right ventricle.

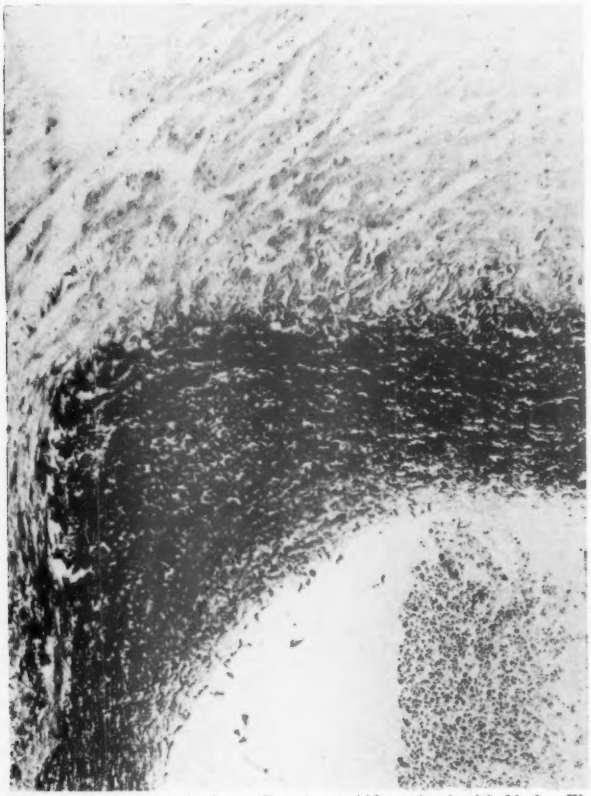

FIG. 3.—Left ventricle from Case 1, × 110, stained with Verhoeff's stain, showing marked thickening and fragmentation of elastic tissue of endocardium.

FIG. 4.—Left auricle from Case 1, × 110, stained to show elastic thickening of endocardium.

Portions of aorta, kidney and spleen were similarly examined to exclude a generalized affection of the vascular tree, but no abnormality was found.

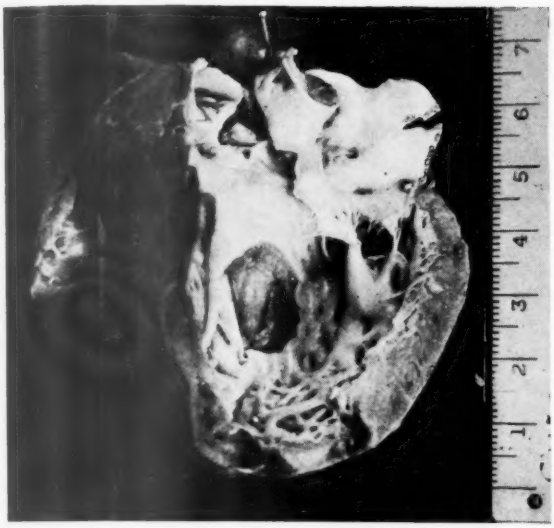

FIG. 5.—Case 2: left side of the heart showing white thickened endocardium.

Case 2. E.C. was admitted on December 28, 1953, with a history of upper respiratory infection for two weeks; dyspnoea and refusal of feeds had been noted for two days. As had been expected from the findings in her twin, cardiac failure was present. She was pale and dyspnoeic, with cyanosis of the mucous membranes. There was some rib recession, the breath sounds being harsh and vesicular, but no râles were heard. The neck veins were slightly distended and the pulse rate was 200 per minute. No cardiac murmurs were heard. The liver was enlarged two fingerbreadths below the costal margin and there was no oedema.

Again there was a good response to digoxin with temporary improvement.

Blood examination showed: Hb 78% (11·5 g. per 100 ml.), W.B.C. 7,400 per c.mm. with a normal differential count. The E.C.G. on admission showed ventricular extra-systoles and that the heart was in an indeterminate position. An E.C.G. three weeks later showed no special ventricular preponderance. Radiographs of the chest and a barium swallow showed an identical appearance to that found in the other twin.

The baby had two further episodes of cardiac failure with temporary improvement from digoxin before dying in cardiac failure at the age of 26½ weeks on February 1, 1954.

NECROPSY. As before, the significant findings were in the chest. The heart was enlarged, its greatest vertical extent being 6 cm. and its greatest width being 5·5 cm. It weighed 48 g. (normal = 32 g.). The foramen ovale and ductus arteriosus were closed. There was no valvular abnormality. Both the ventricles were dilated and hypertrophied, the left ventricular muscle being 10 mm. thick (Fig. 5) and that of the right ventricle 3·5 mm. thick (Fig. 6). The endocardium of the left side of the heart was of a dense white appearance and seemed thickened.

HISTOLOGY. Extensive examination showed that the abnormalities were confined to the endocardium of the left side of the heart which showed a great increase in the number of elastic fibres, the fibres being short and fragmented. Again the left auricular endocardium was that most markedly involved.

Comment

Endocardial fibro-elastosis is reported to be one of the commoner causes of otherwise unexplained cardiac failure and idiopathic cardiac hypertrophy in infants. It is at least as common as idiopathic myocarditis of the Fiedler group and far commoner than glycogen storage disease and anomalies of the coronary arteries (Rosenbaum, Nadas and Neuhauser, 1953). In our experience it is by no means a rare event and we have seen four other cases in the past nine months. Gowing in a recent review confirms this opinion (Gowing, 1953).

The diagnosis should therefore be suspected in any infant presenting with otherwise unexplained cardiac failure, particularly if no murmurs are heard. Partial confirmation can often be obtained by finding left auricular enlargement on x-ray screening. This has already been noted by others (Freer and

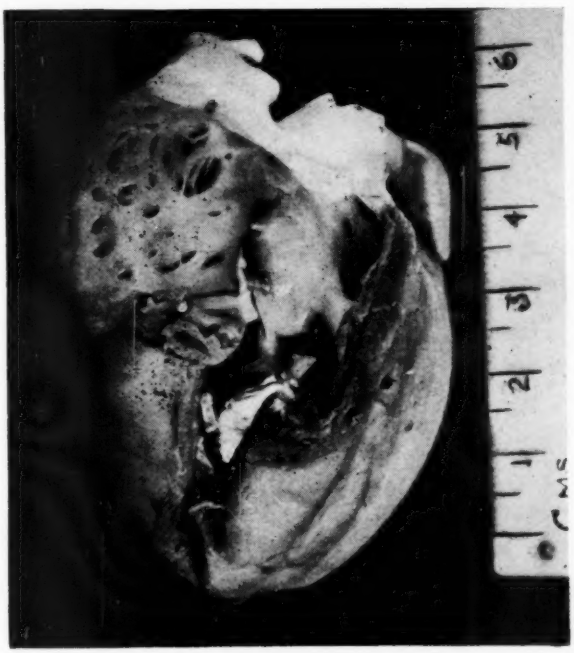

FIG. 6.—Case 2: right ventricle showing relatively normal endocardium.

Matheson, 1953). The differentiation from idiopathic myocarditis may, however, be impossible during life. In our experience electrocardiographic examination has not proved as diagnostically helpful as has been suggested (Adams and Katz, 1952).

Once cardiac failure due to endocardial fibroelastosis has occurred, the clinical course seems to be almost invariably downhill, with temporary remissions, the total duration of symptoms in the majority of cases being under six months (Blumberg and Lyon, 1952).

The concept of the disease has been ably reviewed by others (Gross, 1941; Gowing, 1953). Both writers agree that a developmental anomaly is the most likely cause of the condition and that there is no evidence that infection plays a causative role, although an attack of respiratory or other infection may herald the first onset of cardiac failure. Johnson (1952) suggested that anoxia of the left side of the heart due to premature closure of the foramen ovale accounted for the left side being that mainly involved, and our findings would agree with this idea but cannot be said to prove it since the patients died so long after birth. In our cases, however, there was no evidence of valvular deformity or abnormality of the coronary arteries. In neither of our cases and in none of the other cases seen in this area has there been any evidence of endocarditis or myocardial infection. We feel that the striking similarity shown by the lesions in these twins' hearts, together with the lack of any signs of inflammation, strongly supports a developmental cause for this condition.

Summary

Endocardial fibro-elastosis in identical twins is reported. Previous reports of its incidence in siblings are referred to.

The condition does not seem so uncommon as has been thought.

We wish to thank Dr. Doyle for the photographs of the hearts, Dr. Stanley Wray for the photomicrographs, Dr. David Glass for x-raying the patients, Dr. J. J. Tillie for permission to mention other cases admitted under his care and Mr. B. Isserlin for kindly translating the German reference.

References

Adams, F. H. and Katz, B. (1952). *J. Pediat.*, **41**, 141.

Blumberg, R. W. and Lyon, R. A. (1952). *Amer. J. Dis. Child.*, **84**, 291.

Bonham Carter, R. E. (1954). Personal communication.

Coppoletta, J. M. and Wolbach, S. B. (1933). *Amer. J. Path.*, **9**, 55.

Freer, J. L. and Matheson, W. J. (1953). *Archives of Disease in Childhood*, **28**, 284.

Gowing, N. F. C. (1953). *J. Path. Bact.*, **65**, 13.

Gross, P. (1941). *Arch. Path., Chicago*, **31**, 163.

Johnson, F. R. (1952). *Ibid.*, **54**, 237.

Rosenbaum, H. D., Nadas, A. S. and Neuhauser, E. B. D. (1953). *Amer. J. Dis. Child.*, **86**, 28.

Ullrich, O. (1938). *Z. menschl. Vererb.-u. KonstitLehre*, **21**, 585.

Weinberg, T. and Himelfarb, A. J. (1943). *Bull. Johns Hopk. Hosp.*, **72**, 299.

NON-TRAUMATIC MEDIASTINAL EMPHYSEMA IN CHILDHOOD

BY

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(RECEIVED FOR PUBLICATION MAY 19, 1954)

This condition has been described as occurring in both adults and children and is probably uncommon rather than rare. There are few recorded cases in the British paediatric literature, but in discussion of the subject with colleagues occasional instances in children have been mentioned.

In the absence of the associated subcutaneous emphysema the mediastinal collection of air is likely to be overlooked clinically, but the increased resort to radiography in acute chest illness may well reveal that it is not so very uncommon as a complication.

After a perusal of the literature it was considered of interest that four patients—one infant and three children—had been encountered in a short period of time. In these patients the condition had not come within either the spontaneous or the traumatic groups but was secondary to recognized pulmonary illness.

Case Reports

Case 1. J.G., a girl, aged 10 months, was admitted to hospital in the third week of pertussis because of a convulsion and developed a measles rash the day following. Eleven days later a widespread subcutaneous emphysema was seen which involved the whole of the upper thorax and extended to the face, neck and scalp. The infant was cyanosed, dyspnoeic and ill, with an exhausting cough before this emphysema was noted, and its onset had not been preceded by any noticeable deterioration in her condition.

Radiographs confirmed the presence of mediastinal and subcutaneous emphysema associated with areas of lobular collapse and consolidation in both lung fields. There was no pneumothorax.

The emphysema took three weeks to absorb completely. The infant eventually recovered after a stormy illness which included a second bronchopneumonic episode, without complications.

The complication of measles in the third week of a severe pertussis infection provided the requisite conditions for the development of either a pneumothorax or mediastinal emphysema. The forced expiratory explosions of the whooping cough and the inflammatory pulmonary lesions of the measles caused what was probably, from the degree and extent of the emphysema, a considerable pulmonary rent.

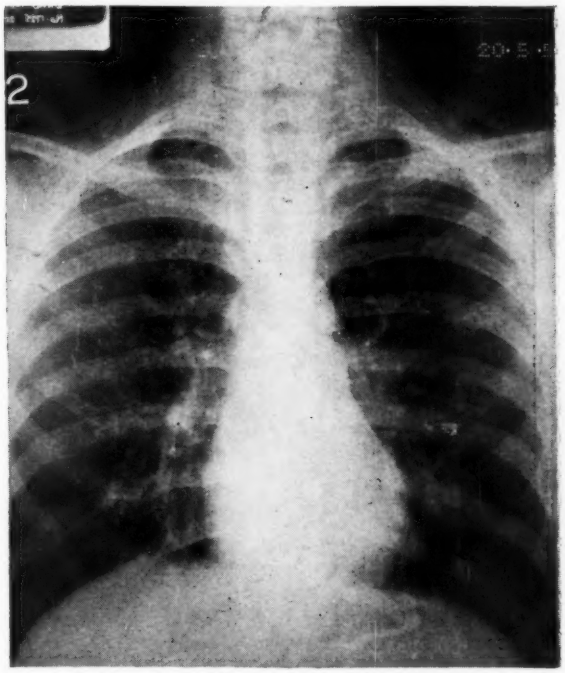

FIG. 1.—Radiograph showing double contour of the left border of the heart and subcutaneous emphysema of the neck.

Case 2. D.J., a boy, aged 13 years, had suffered from asthma since infancy. Two days before we saw him he had had a severe asthmatic episode with much retching and vomiting. He complained of a sharp substernal pain of brief duration during the attack. He saw his doctor next day because of swelling of the neck which was recognized as subcutaneous emphysema and he was referred to hospital.

Clinically the boy was not acutely ill. He had subcutaneous emphysema mainly confined to the supraclavicular regions. The superficial area of cardiac

dullness was diminished and the heart sounds were distant. There was general hyper-resonance to percussion and the breath sounds were diminished throughout the lung fields.

Radiologically there were emphysematous changes in both lung fields with a double contour round the left border of the heart. Oblique and lateral views showed the air in the mediastinum to extend into the root of the neck, and there was evidence of air in the superficial tissues of the supraclavicular regions (Fig. 1).

The lungs were emphysematous due to long-standing asthma, and an acute asthmatic attack with straining and vomiting was followed by mediastinal and subcutaneous emphysema.

Case 3. J.B., a girl, aged 2½ years, was admitted to hospital on the third day of an acute respiratory illness with a temperature of 104° F. Constitutional symptoms were predominant and cough was not noticeably troublesome. A clinical diagnosis of pneumonia in the right lung was made and the child was nursed in an oxygen tent and given antibiotics.

The day after admission a crepitant swelling appeared in the suprasternal region (Fig. 2). This increased in size during that day and then gradually subsided.

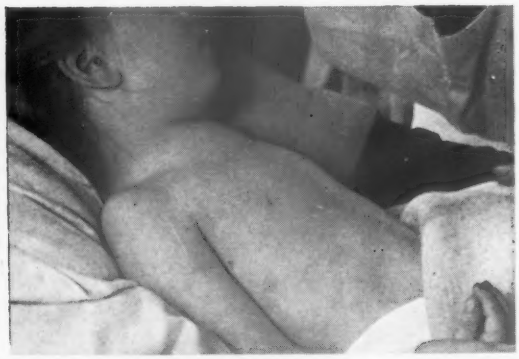

FIG. 2.—Photograph showing distension of the suprasternal region by subcutaneous air.

Radiographs taken two days after the appearance of the subcutaneous emphysema showed patchy consolidation of the left lower lobe, collapse of the right middle lobe and mediastinal and subcutaneous emphysema; the latter was mainly in the upper thorax and neck.

The child was apyrexial by the ninth day of illness and made an uncomplicated recovery.

The sequence was that of a bronchopneumonia complicated by lobar collapse with pulmonary emphysema, air escaping into the interstitial portion of the lung with consequent mediastinal and subcutaneous emphysema.

Case 4. M.W., a girl, aged 5 years, was very well up to 48 hours before admission to hospital. Her illness began without fever or coryzal symptoms but the child developed a persistent cough which was very troublesome at night but less so during the day when she was not confined to bed. There was no constitutional upset.

On the day of admission (the third day of symptoms) she was 'a little weary' but was not dyspnoeic or cyanosed; she appeared however to be afraid to take a very deep breath.

At this stage the family doctor was consulted, detected subcutaneous emphysema, and sent the patient to hospital.

On admission the relevant clinical findings were of a not acutely ill child. The temperature was 99° F.; pulse 112, and there was no dyspnoea, cough or cyanosis. There was subcutaneous emphysema of the upper thorax, including the axillae, and extending into the cervical region. The loud crackling of the emphysema obscured the breath sounds. It was not possible to localize the apex beat and the heart sounds were distant.

In 24 hours the subcutaneous emphysema had spread considerably and had reached the parotid area on the right side. Thereafter it gradually disappeared and was undetectable clinically by the sixth day after admission.

Of the investigations carried out the only relevant findings were a slightly raised blood sedimentation rate (18 mm. in one hour by micro method) and a total leucocyte count of 16,600 per c.mm. The Mantoux test (1 in 1,000 old tuberculin) was negative.

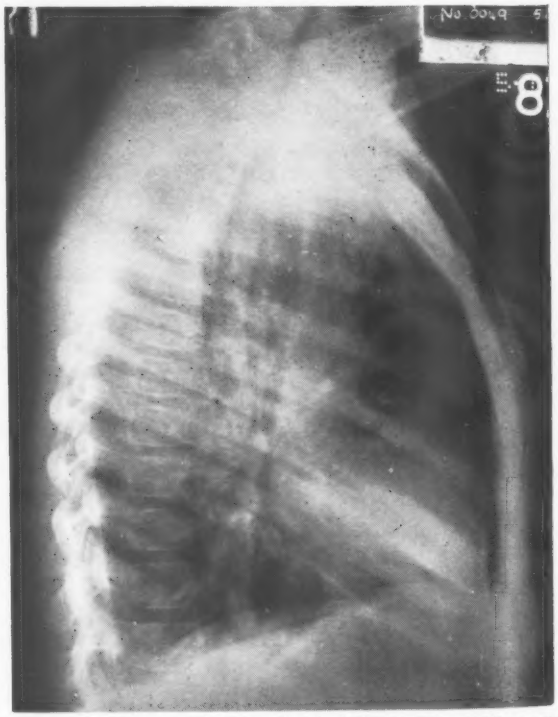

FIG. 3.—Air shown outlining mediastinal structures as well as some superficial to the sternum. Right middle lobe collapse is also evident.

Radiographs (Figs. 3 and 4) taken on the third day following the appearance of subcutaneous emphysema showed collapse of the right middle lobe with marked emphysema outlining the structures of the anterior mediastinum particularly well in the lateral view of the chest. This projection also demonstrated subcutaneous emphysema lying anteriorly to the sternum. A postero-anterior view of the chest showed air in the superficial tissues of the neck, whilst a lateral view showed the air to have extended into the pre-cervical fascia.

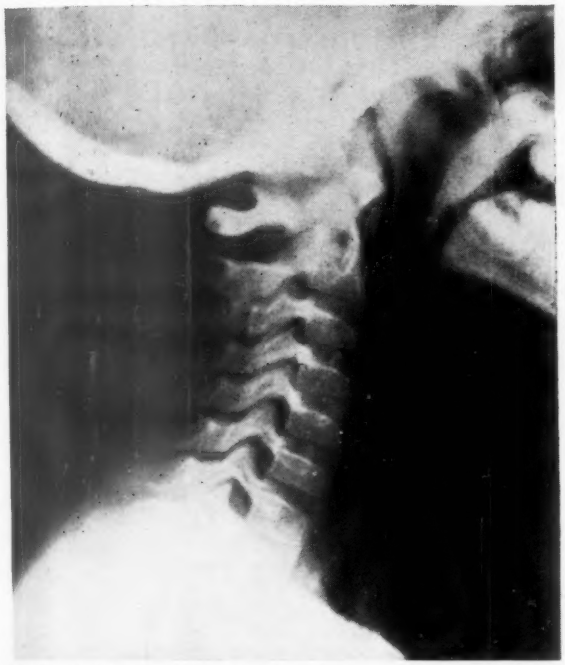

FIG. 4.—A lateral radiograph shows air in soft tissue planes of the neck.

Two weeks from the onset of the illness the chest radiograph was within the bounds of normal.

The sequence of events was a probable tracheitis with a persistent cough producing collapse of the right middle lobe and subsequent pulmonary, mediastinal and subcutaneous emphysema.

Radiological Features

The precursor of non-traumatic mediastinal emphysema is almost invariably pulmonary interstitial emphysema, and since the radiological features of this condition have recently been very fully described by Herrnheiser and Whitehead (1953) they will not now be discussed.

When a minor degree of mediastinal emphysema is present this extra-pulmonary air may not be observed in the routine postero-anterior view of the chest, and oblique or lateral projections are necessary to demonstrate it. These smaller amounts of air are generally shown as streaky shadows in the anterior and posterior mediastina. They accentuate the outlines of the vessels and organs in those areas, more particularly the anterior border of the heart, the thymus in children, and the aorta and the great vessels, extending even up into the root of the neck. In one of our cases the apex of the heart was clearly outlined, and the air accentuated its diaphragmatic border. An associated pneumothorax is not common with this degree of pneumomediastinum.

When a larger amount of air has found its way into the mediastinum it is generally readily seen in the postero-anterior radiograph as a double contour round a portion of the cardiac shadow. It often tracks up into the soft tissues of the neck, either in the compartments of the great vessels, behind the sternum anteriorly, or posteriorly into the space between the prevertebral fascia of the neck and the pharynx. A pneumothorax, which, if present, is almost invariably left sided, may cloak these radiological appearances to some degree.

In the very severe cases where the mediastinal air is present in large amounts, the cardiac shadow may appear to be smaller than normal and to be displaced. The sternum may appear to be bulged forward.

The air may be shown radiologically to be extensively spread in the superficial tissues, and this extension may relieve the pressure on the heart and the great vessels.

Careful note should be taken of any radiological changes in the lung fields of these cases, particularly findings suggestive of asthma and lobar or lobular collapse.

It is considered that the proportion of cases in which the air is seen in the superficial tissues is higher in children than in adults.

Theories of Aetiology

Pneumomediastinum was described before the days of Laennec, and Müller in 1888 gave a graphic account of the clinical signs. It is, however, on the work of Macklin (1939) and Hamman (1945) that the modern conception of non-traumatic mediastinal emphysema really rests.

Macklin, following experimental work on cats, suggested that hyperinflation of the alveoli bordering on blood vessels tended to build up an intra-alveolar pressure greater than that within these vessels, causing a rupture of the alveolar bases and escape of air into the perivascular sheaths. These tiny bubbles of air passed down the sheaths towards the hilum, and, tending to coalesce, formed blebs of air in the hilar region whence they burst into the mediastinum. In addition Macklin considered that there were extensions of air into the contiguous

connective tissue formations in the region of the hila. This mechanism not only caused a degree of vascular stasis due to the air in the perivascular sheaths occluding the vessels, but reduced the respiratory excursion by 'splinting' the lung tissue. This conception of the mechanism of the formation of non-traumatic pneumomediastinum has now been widely accepted.

When the air reaches the mediastinum there are three possible courses open to it. (1) It may remain within the mediastinum and build up a pressure which will cause partial occlusion of the great vessels and consequent cardiac embarrassment and dyspnoea. (2) In approximately a third of the cases a pneumothorax occurs, which Macklin considers may be caused by air from the mediastinum, though he does not consider that the air from a pneumothorax can travel in the opposite direction. (3) The air may track up into the superficial and deep tissue planes in the neck and into the superficial tissues of the thorax and trunk, thus markedly relieving the pressure in the mediastinum.

The condition may be associated with any lesion causing localized atelectatic changes in the lungs which could be surrounded by an area of hyperinflated lung tissue. It is considered that an element of congenital weakness must be present in this lung tissue as well.

Clinical Features

The occurrence of mediastinal emphysema, with or without an associated pneumothorax, is of course well known to the thoracic surgeon. Its appearance following tracheotomy operations has often been described and is readily explained, and non-operative pulmonary trauma from missiles and blast has provided a number of cases in recent years.

Another group, spontaneous mediastinal emphysema, has been so called because it occurs in previously healthy individuals in whom no underlying pathological condition can be demonstrated. This group is important since, being uncomplicated by trauma or associated pathological cause, its symptoms and signs are those of mediastinal emphysema *per se*. These are the sudden onset of chest pain and dyspnoea with an absence of constitutional symptoms. In about half these cases there is also an associated spontaneous pneumothorax.

Clinically, about a quarter of these spontaneous cases have subcutaneous emphysema. The area of cardiac dullness is diminished, but the characteristic feature is a peculiar sound over the cardiac region. It is known as Hamman's sign and is variously described as 'crunching', 'crackling', 'clicking', 'like the rattling of dried peas on taut canvas' or 'the crinkling of a newspaper'. It is heard throughout the respiratory cycle and may even be audible to the patient himself.

Our four cases, being children, were unable to describe their symptoms adequately, though the boy of 13 did complain of sharp chest pain. All had some underlying illness the symptoms of which obscured the onset of the mediastinal emphysema. It seems likely that if the mediastinal air is able to escape before much intra-mediastinal pressure is built up, then acute subjective symptoms may be minimal or absent. The subcutaneous spread of air is an escape way.

In two of our cases it was possible to estimate that they were in no way inconvenienced by the air in the mediastinum. One patient walked quite a distance to the Out-patient Department, and the other was referred to hospital because her doctor recognized the presence of something unusual and not because she was seriously ill.

In none of our cases was Hamman's sign detected. Previous authors have emphasized that it is by no means always present and is seldom detected in infants and young children. Draper (1948), however, found the sign in 90% of the spontaneous variety, and we suspect that the high incidence of associated left-sided pneumothorax in those cases may be responsible for helping to bring out the characteristic sounds.

Treatment

We have no comment to offer on treatment.

Our patients required therapy only for the underlying pathological condition. From our small experience we might agree with the dictum that mediastinal emphysema 'is a relatively harmless condition'.

Summary

The relevant clinical and radiological features of four cases of non-traumatic mediastinal emphysema are presented.

The aetiological and mechanistic theories are discussed.

We should like to acknowledge with thanks the courtesy of Dr. S. K. Guthrie of the Duchess of York Hospital for Babies and Dr. D. C. Liddle of Monsall Hospital, Manchester, for allowing us to use cases which had been under their care; Dr. J. Wraith, for the loan of the radiographs, and Mr. Ward for the photograph.

References

Draper, A. J. (1948). *Amer. J. Med.*, **5**, 59.
Hamman, L. (1945). *J. Amer. med. Ass.*, **128**, 1.
Herrnheiser, G. and Whitehead, J. P. (1953). *Brit. J. Radiol.*, **26**, 519.
Macklin, C. C. (1939). *Arch. intern. Med.*, **64**, 913.

INTESTINAL POLYPOSIS ASSOCIATED WITH MELANOSIS ORIS

BY

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(RECEIVED FOR PUBLICATION MAY 18, 1954)

Weber (1919) described a case of acute intussusception in one of a pair of twins originally noticed by Hutchinson (1896) to have oral pigmentation. Peutz (1921) recorded a family of seven, and Jeghers, McKusick and Katz (1949) reported 10 cases of melanosis of the lips and buccal mucosa together with polyposis of the gastro-intestinal tract. The latter's report included a review of the literature. Since then 45 cases have been recorded in the world literature, 15 of these in England (Foster, 1944; Tanner, 1951; Wolff, 1952; Kitchin, 1953; Hunter and Wilson, 1953; Smith, 1954; Savage, 1954; Young, 1954; Walker-Brash, 1954; Crone and Light, 1954). The case recorded here is probably an example of this syndrome although not yet proven.

Case Report

The patient, a boy with a fair complexion, was born in August, 1951. He began vomiting almost from birth and on the third day produced 'coffee grounds'. In October, 1951, he was admitted to hospital on account of an exacerbation of the vomiting. Pyloric stenosis was diagnosed and the child was treated medically, but the vomiting persisted. A barium meal examination in December showed no abnormality. In March, 1952, he again vomited brownish material and a second barium meal examination then suggested a small hiatus hernia. In June, 1952, the vomiting was worse for a short period and in December a third barium meal showed no change. He was readmitted to hospital in March, 1953, with vomiting and attacks of colicky abdominal pain; no cause was found. After a symptom-free period of one year, he again began vomiting with attacks of colicky abdominal pain and, for the first time, passed bright red blood in the stools for two days. A barium meal with a follow-through examination and two sigmoidoscopies were normal. The haemoglobin was 86 g. %; the urine showed no melanin or melanogen, and the test for occult blood in his stools was negative. A week later he had a further bout of colicky abdominal pain and more fresh blood was passed per rectum. Sigmoidoscopy to 14 cm. again showed no polyposis. In view of the child's age it was not felt justified to proceed with further air-and-barium contrast or sigmoidoscopic studies.

His mother was the first to notice the inky to brown pigmentation on the lower lip at 5 months of age. It is now visible on the gums between the right lower pre-molars, on the lower lip, the upper lip, the right temporal region, the right side of the neck, and it has a butterfly distribution over the nasal bridge (Fig. 1). The

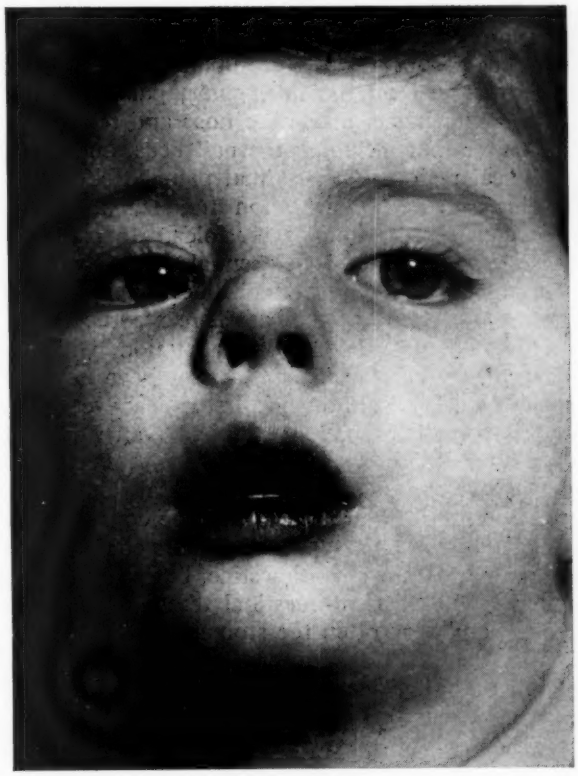

FIG. 1.—Pigmented lips.

mother, a State Registered nurse and a reliable witness, is convinced that the pigmentation increases during a bout of symptoms, and an attack at the time of writing would appear to confirm this. No pigmentation is present on the extremities, around the penis, in the fundi, ears, conjunctivae or nose.

His elder brother has a butterfly pigmentation of the nasal bridge and a pigmented patch in the right axilla together with a large area over the left deltoid. He has never had any symptoms. A grandmother had died of malignant changes in papillomatosis of the bladder.

Discussion

The syndrome, having an equal sex distribution and often familial, is believed to be genetically determined by a simple Mendelian dominant, the factors being transmitted equally by men and women. Sporadic cases, however, do occur as in the patients of Perry and Zuska (1950), of Schaffer and Sachs (1952) and of Smith (1954). It has been recorded in white people of many countries, in an American negro (Jeghers *et al.*, 1949), and in an Indian woman, many members of whose family only had the pigmentation (Basu, 1952). Tanner (1951) stated that all cases had a dark complexion but since then Kitchin's (1953) and the above case are reported as of light complexions. The pigmentation, shown by biopsy to be due to melanin, varies from a brown to a deep bluish-black and has been recorded on the lips, gums, palate, tongue, face, conjunctivae, inside the nose and rectum, on the extremities including the nail beds, and in the umbilical region. The normal pigment sites show no increase of pigmentation nor has any been recorded in the natural body folds. In particular the buccal lesions appear essential to the syndrome to exclude the diagnosis of ephelides (freckles). An interesting feature of the case here recorded is the waxing and waning of pigmentation with the symptoms. The facial pigmentation regresses with age (Peutz, 1921) although it first appears very early and is sometimes present at birth (van Dijk and Oudendal, 1925; Jeghers *et al.*, 1949; Perry and Zuska, 1950). The buccal mucosal and labial pigmentation, however, is said to be constant.

Polyposis in this syndrome occurs chiefly in the jejunal part of the small intestine, but also throughout the whole gastro-intestinal tract including the rectum and very often the stomach (Jeghers *et al.*, 1949; Tanner, 1951; Bruwer, Bargen and Kierland, 1954), the latter accounting for haematemesis as a rare presenting symptom. Polyps have also been recorded in the nose and bladder (Peutz, 1921). Polyps can occur without pigmentation (Ravitch, 1948), just as pigmentation can occur without symptoms or evidence of polyposis (Touraine and Couder, 1946; Jeghers *et al.*, 1949), but these cases may not belong to this syndrome. Oldfield (1954) has described polyposis in three members of a family associated with multiple sebaceous cysts, this syndrome also being inherited as a Mendelian dominant.

The gastro-intestinal signs and symptoms of this syndrome include colicky abdominal pain, vomiting, haematemesis, passing blood per rectum, rectal prolapse and anaemia. In confirming the diagnosis, radiographs taken after a contrast air-and-barium enema may show up polypi not seen by ordinary barium radiography (Bruwer *et al.*, 1954), although most cases have only been diagnosed after laparatomy. A diagnosis of intussusception can be made with confidence when there are symptoms of intestinal obstruction and when the bucca are pigmented (Crone and Light, 1954).

Apart from the adenocarcinomatous changes recorded in six patients (Peutz, 1921; Foster, 1944; Jeghers *et al.*, 1949; Basu, 1952; Smith, 1954), most of the 45 patients suffered from repeated intussusception and many died before or after operation. Thus the long-term prognosis is poor.

Summary

A case is described of melanosis oris associated with some of the symptoms of acute intussusception. A review of the literature discloses a definite syndrome known as the Peutz-Jeghers syndrome consisting of melanosis of the body, especially of the buccal cavity and lips associated with gastro-intestinal polyposis. The patients usually present with small bowel obstruction due to one of the polyps causing an intussusception. Although not conclusively proven, this child's disease would appear to be a further example of this rare syndrome. It is believed that this patient is the youngest on record, and the case is of special interest because the diagnosis was made without operation.

I wish to thank Dr. E. Hinden for permission to publish this case and for his and Dr. R. Calvert's help and encouragement in preparing this paper.

References

Basu, A. K. (1952). *Lancet*, **2**, 586.
Bruwer, A., Bargen, J. A. and Kierland, R. R. (1954). *Proc. Mayo Clin.*, **29**, 168.
Crone, W. P. and Light, A. L. (1954). *Brit. med. J.*, **1**, 1133.
Dijk, J. A. van and Oudendal, A. J. F. (1925). *Ned. T. Geneesk.*, **69** (1), 966.
Foster, D. B. E. (1944). *Ibid.*, **2**, 78.
Hunter, W. R. and Wilson, W. A. (1953). *Brit. J. Surg.*, **40**, 521.
Hutchinson, J. (1896). *Arch. Surg., Lond.*, **7**, 290.
Jeghers, H., McKusick, V. A. and Katz, K. H. (1949). *New Engl. J. Med.*, **241**, 993.
Kitchin, A. P. (1953). *Brit. med. J.*, **1**, 658.
Oldfield, M. C. (1954). *Brit. J. Surg.*, **41**, 534.
Perry, B. F. and Zuska, J. J. (1950). *U.S. armed Forces med. J.*, **1**, 773.
Peutz, J. L. A. (1921). *Ned. Maandschr. Geneesk.*, **10**, 134.
Ravitch, M. M. (1948). *Ann. Surg.*, **128**, 283.
Savage, C. R. (1954). *Brit. J. Surg.*, **41**, 366.
Schaffer, A. B. and Sachs, S. W. (1952). *Oral Surg.*, **5**, 271.
Smith, M. (1954). *Brit. J. Surg.*, **41**, 367.
Tanner, N. C. (1951). *Proc. roy. Soc. Med.*, **44**, 405.
Touraine, A. and Couder, F. (1946). *Presse méd.*, **54**, 405.
Walker-Brash, R. M. T. (1954). *Brit. med. J.*, **1**, 1132.
Weber, F. P. Parkes (1919). *Quart. J. Med.*, **12**, 404.
Wolff, H. H. (1952). *Lancet*, **1**, 446.
Young, H. B. (1954). *Edinb. med. J.*, **61**, 122.

ATYPICAL CONGENITAL HAEMOLYTIC ANAEMIA

BY

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(RECEIVED FOR PUBLICATION APRIL 26, 1954)

The most common type of congenital haemolytic anaemia found in Great Britain is familial haemolytic anaemia (chronic acholuric jaundice). A similar congenital haemolytic anaemia may be found on rare occasions in children in whom the red cells do not show spherocytosis, or increased osmotic fragility. The response to splenectomy is not very satisfactory and the syndrome does not fit into the established pattern of familial haemolytic anaemia. Cases of this type have already been described by Haden (1947), Crosby (1950), Kaplan and Zuelzer (1950) and by Dacie, Mollison, Richardson, Selwyn and Shapiro (1953). The following is a further example of this atypical (non-spherocytic) congenital haemolytic anaemia.

Case Report

A girl aged 7 was the fourth child in a family of five. Her mother died of metastases from a melanotic sarcoma a few months after the birth of her fifth child. The patient as a baby was noticed to be pale and on occasions mildly jaundiced. She failed to gain weight and walked late. On one occasion she was admitted to hospital with rickets from which she made a complete recovery. From the age of 6 she was noticed to be pale, listless, jaundiced and had definite abdominal swelling. She was admitted to hospital.

On examination the child had a definite mongoloid facies (Fig. 1). All the mucous membranes were pale and there was moderate jaundice. The cervical lymph nodes were slightly enlarged. No bony deformity resulting from rickets could be detected. The spleen was enlarged and the liver palpable. There was a soft, non-conducted mitral systolic murmur.

The haemoglobin was 34% Haldane (4·6 g./100 ml.), erythrocytes 1·32 million per c.mm., colour index 1·3, P.C.V. 15%, M.C.V. 94 cubic microns, M.C.H.C. 30%, leucocytes 4,100 per c.mm. (neutrophil polymorphs 62%, lymphocytes 35%, monocytes 3%), reticulocytes 17%, normoblasts=13/100 white blood cells. A film showed some macrocytosis, anisocytosis and polychromasia. There was no evidence of spherocytosis, fragmentation or bizarrely shaped erythrocytes. The osmotic fragility of erythrocytes (room temperature) was normal on repeated examination. The Coombs test was negative. The serum bilirubin was 3·75 mg./100 ml. Serological tests for syphilis were negative. No auto-agglutinins or haemolysins could be detected in the serum and the titre of cold agglutinins was 1 in 8.

The bone marrow showed a marked normoblastic hyperplasia, 58·5% of cells belonging to the erythropoietic series.

General cardiac enlargement was seen on radiological examination of the chest but no evidence of pulmonary disease.

Radiographs showed bony changes in the skull. These changes were largely confined to the frontal and parietal regions of the calvarium and consisted of a great thickening of the diploe with vertical striations and atrophy of the outer table (Fig. 2). The horizontal table of the frontal bones was thickened. No evidence of brachyphalangia or any change in the intimate bony structure was shown on radiological examination of the hands.

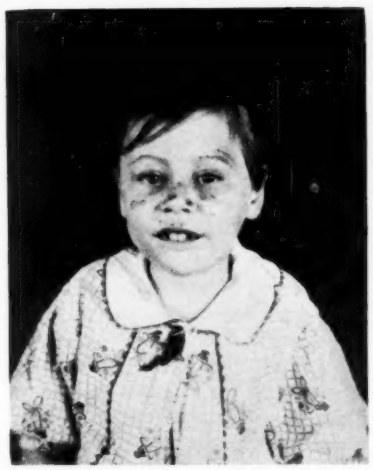

FIG. 1.—Photograph of the patient showing the mongoloid-like facies.

The spleen was removed in October, 1948.

Histological examination of the spleen did not reveal the changes normally associated with familial haemolytic anaemia. The lymph follicles were separated by a cellular but uncongested pulp. The splenic sinusoids were prominent and lined by large littoral cells. There

was an increase of reticulum cells with vesicular nuclei throughout the pulp cords with a slight increase of the connective tissue elements, but erythrophagocytosis and extramedullary haemopoiesis could not be demonstrated. Occasional haemosiderin-laden macrophages were present in the pulp cords but not in the supporting tissues.

The child has been observed for four years since splenectomy, during which time she has developed normally, has attended school regularly, and has engaged in the usual childhood pursuits. Anaemia has persisted although it is less marked than before operation (Table 1). Jaundice and hepatomegaly have remained but not increased. The apical systolic bruit is still present. The haemoglobin has varied between 57% (8·4 g./100 ml.) and 75% (11·1 g./100 ml.) and the erythrocytes between

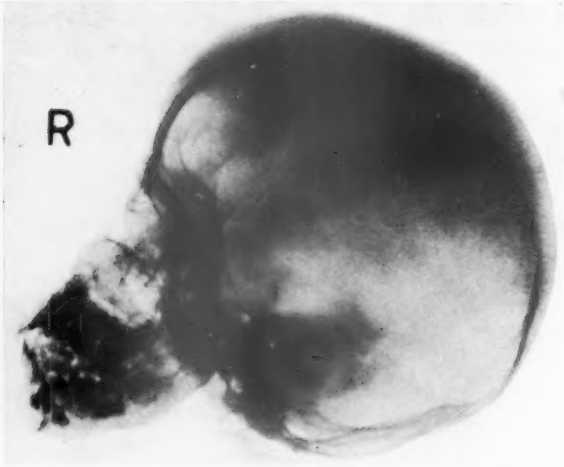

FIG. 2.—Radiograph of the skull showing the thickened diploe, 'hair-on-end' appearance and atrophy of the outer table.

2·25 and 3·05 millions per c.mm., with a high colour index. The M.C.V. has remained high but the M.C.H.C. normal. There has been a constant high reticulocyte count (18-39%) and a hyperbilirubinaemia. Normoblasts have been persistently in the peripheral blood and their number has been roughly correlated with the degree of reticulocytosis. Leucocytosis and thrombocytosis have marked the post-splenectomy peripheral blood findings.

A study of the survival of transfused erythrocytes in the patient was undertaken after splenectomy. This showed a steady decline in the transfused cells which were destroyed at the normal rate. The survival of the patient's cells in a normal individual was not undertaken.

Four years after splenectomy the child received a therapeutic trial of 150 mg. cortisone daily for eight days. Thereafter the dose was gradually reduced by 25 mg. every 48 hours. (The total dose given was 1·7 g. in 16 days.) This produced an entirely non-specific response with evidence of marrow stimulation, as shown by a leucocytosis, thrombocytosis, increased reticulocytosis and normoblastosis. However, the erythrocyte count per c.mm. of whole blood showed no significant change, and the jaundice did not deepen. A fluid retention hydraemia resulting from the cortisone therapy may have masked a true increase in the total number of circulating red cells which might have been expected in view of the reticulocytic response. There may have been a true increase in the total circulating red cell mass but blood volume studies were not made to confirm this.

Comment

From birth this patient had a severe anaemia associated with mild jaundice and splenomegaly. There were no episodes of crisis. The anaemia was haemolytic in character as evidenced by the constant reticulocytosis, the presence of normoblasts in the peripheral blood, the hyperbilirubinaemia and the normoblastic hyperplasia of the bone marrow. Spherocytosis of erythrocytes could not be demonstrated and the red cell osmotic fragility was normal on repeated testing.

The differential diagnosis from other congenital haemolytic anaemias was considered. The absence of crises, spherocytosis and increased osmotic fragility was thought to exclude familial haemolytic anaemia. No sickling of erythrocytes could be demonstrated. The anaemia was not hypochromic in character, target cells were not seen in the peripheral blood, and the osmotic resistance of the red cells was not increased as in Mediterranean anaemia. The possibility of a symptomatic haemolytic anaemia was also considered. In this condition, however, the blood picture resembles familial haemolytic anaemia and there is a definite relationship to an underlying disease such as leukaemia, Hodgkin's disease or neoplasm. Allibone and Collins (1951) recorded a case of severe haemolytic anaemia in a girl of 4 which was cured by the removal of a cystic teratoma from the ovary. In the present case clinical, haematological and radiological investigations failed to reveal any underlying disease to which the haemolytic anaemia could be considered as secondary. Consequently the condition was regarded as congenital non-spherocytic haemolytic anaemia.

The tendency towards the development of a facial configuration of mongoloid type was noted in this case and in those described by Kaplan and Zuelzer (1950). The presence of osseous changes was a marked feature. These changes consisted of a thickening of the calvarium of the frontal and parietal bones with a 'hair-on-end' appearance. The short tubular bones were unaffected. In previous reports the familial and hereditary nature of this disease has been described, but it could not be confirmed in this instance.

The response to splenectomy serves to differentiate

TABLE I

BLOOD PICTURE BEFORE AND AFTER SPLENECTOMY

Date	Haemoglobin (g./100 ml.)	Erythrocytes ($\times 10^6$/c.mm.)	M.C.V. (c. micron)	Leucocytes (per c.mm.)	Reticulocytes (%)	Bilirubin (mg. %)	Normoblasts (per 100 W.B.C.s)
13/5/48	4·6	1·32	94	4,100	17	1·0	—
10/7/48	2·8	0·73	123	4,800	15	3·5	13
24/9/48	7·4	1·96	120	4,350	3	—	—
Splenectomy (October 29, 1948)							
18/11/48	10·1	2·83	114	10,700	—	—	—
25/5/49	9·8	2·95	100	9,100	18	2·5	6
29/4/50	9·5	2·65	102	17,750	30	1·6	6
5/12/51	8·4	2·47	106	11,400	30	1·25	12
3/10/52	9·6	2·36	113	8,500	25	2·5	7

this disease from familial haemolytic anaemia. Splenectomy in the latter condition is uniformly beneficial and is rapidly followed by a loss of all evidence of excessive haemolysis. In congenital non-spherocytic haemolytic anaemia removal of the spleen may be followed, as in this case and in one described by Dacie *et al.* (1952), by some improvement in the anaemia but the reticulocytosis, normoblastosis and bilirubinaemia persist. The macrocytosis was unaffected by splenectomy (Table 1).

In the post-splenectomy period cortisone therapy had no effect on the haemolytic anaemia. The response obtained was non-specific and similar to that produced in normal human beings. Cortisone treatment in familial haemolytic anaemia is not beneficial but in many cases of acquired haemolytic anaemia a profound, if temporary, improvement is obtained. This consists in a decrease in the severity of blood destruction with a rise in the haemoglobin and a fall in the reticulocyte and bilirubin level of the peripheral blood.

Despite the absence of any morphological change in shape of the erythrocytes it is considered that the defect in this condition is intra-corpuscular. This is inferred from the inability to demonstrate either circulating immune bodies in the serum of these cases or adsorbed antibody on the erythrocytes using the Coombs test. The demonstration that the survival of erythrocytes transfused from these patients into normal individuals is markedly shortened whereas normal erythrocytes transfused into them survive normally (Crosby, 1950; Kaplan and Zuelzer, 1950) is further evidence in support of an intra-corpuscular defect.

Summary

A case of congenital non-spherocytic haemolytic anaemia is described.

Clinically the disease was characterized by anaemia, jaundice, hepatosplenomegaly, osseous changes and a mongoloid-like facies. Crises were absent.

The erythrocytes were macrocytic, showed no spherocytosis and had a normal osmotic fragility.

The anaemia improved following splenectomy although haemolysis continued. The post-splenectomy haemolysis was unaffected by cortisone therapy.

I wish to thank Dr. H. Hilton Stewart, of the Ulster Hospital, for the clinical details of this case and the Northern Ireland Hospitals Authority for a research grant.

REFERENCES

Allibone, E. C. and Collins, D. H. (1951). *J. clin. Path.*, **4**, 412.
Crosby, W. H. (1950). *Blood*, **5**, 233.
Dacie, J. V., Mollison, P. L., Richardson, N., Selwyn, J. G. and Shapiro, L. (1953). *Quart. J. Med.*, **22**, 79.
Haden, R. L. (1947). *Amer. J. med. Sci.*, **214**, 255.
Kaplan, E. and Zuelzer, W. W. (1950). *Blood*, **5**, 811.

MICTURATING CYSTO-URETHROGRAPHY IN THE INVESTIGATION OF ENURESIS

BY

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(RECEIVED FOR PUBLICATION MAY 3, 1954)

Enuresis is an important human problem. The persistence of the disability is regarded with despair by parents, while the patients' distress and embarrassment are difficult to assess. In spite of investigations and treatment by paediatricians, urologists and psychiatrists there is still no reliable cure.

During a period of post-graduate study in Stockholm one of us became interested in a new cysto-urethrographic technique in process of development by Kjelberg and Rudhe. We considered that the technique might, with modification, be a valuable means of investigating cases of persistent enuresis. The simple cysto-urethrographic technique described below is largely due to the inspiration and help provided by our Swedish colleagues. Examination of the urinary tract by ordinary methods does not, as a rule, reveal any abnormality, but this method of investigation has shown that there is in fact a surprisingly high incidence of organic abnormalities in enuretic children.

Enuresis may be defined as the involuntary discharge of urine and it assumes clinical importance in a child over 3 years of age. It is usually nocturnal but may be either diurnal and nocturnal, or diurnal alone. The incidence of enuresis in childhood varies with many factors such as age, environment, heredity, legitimacy, etc. Sheldon (1944) in a series of 5,000 children from residential homes between 5 and 10 years of age reported 5% to be suffering from enuresis. Thorne (1944) studied 1,000 army recruits and found that 16% gave a history of enuresis after 5 years of age. Despert (1944) showed that of 1,000 unselected children between 4 and 12 years of age enuresis was present in 26%. These figures show that enuresis occurs in 5 to 25% of children between the ages of 4 and 12 years. From an examination of army recruits the incidence of enuresis in adult males was reported by Cohen (1947) to be as high as 2·5% in U.S. army recruits. It is reasonable to assume therefore that as the majority of enuretic children recover, their condition is functional in origin. The remainder, which form about 10%, persist and are likely to have some organic disorder.

Most paediatric textbooks infer that organic disease can be excluded if a careful history is taken and an adequate examination of the patient and the urine made; on the other hand, some textbooks advise examination by a urologist if the enuresis fails to improve with treatment.

It is our experience that in spite of an adequate history and clinical examination the diagnosis of abnormalities of the urinary system is seldom possible unless special investigations, such as micturating cysto-urethrography, are undertaken. Furthermore, such investigations will lead to the earlier diagnosis of urological conditions which, if untreated, may give rise to a far more serious condition than the initial symptom of enuresis.

Investigation of Persistent Enuresis

A study of 135 children with persistent enuresis has been undertaken; all these children were 5 years of age or older and their condition had not responded to at least three months' intensive medical and/or psychiatric treatment. In the investigation of these patients special attention was paid to the history, e.g. age of onset, whether nocturnal, diurnal, or nocturnal and diurnal. The presence of frequency, urgency, straining or dribbling was noted and details of toilet training, attempts at cure, and the parents' and patients' attitude to the condition were determined. The child's development and progress at school were assessed. Attention was paid to the presence or absence of faecal incontinence. The incidence of enuresis in parents and siblings was recorded.

As part of a full clinical examination particular attention was paid to the following: the presence or absence of an enlarged bladder; malformation of the external genitalia; motor and sensory disturbances and the tone of the anal sphincter. The act of micturition was observed, a catheter specimen of

* Holder of a Cow and Gate travelling scholarship at Professor Wallgren's Clinic at Stockholm, 1952-53.

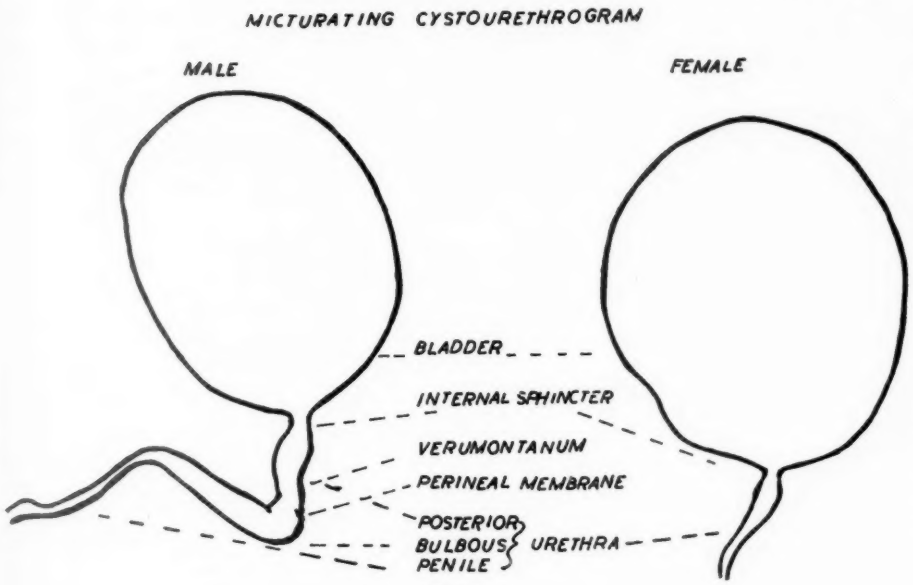

FIG. 1.

urine examined and cultured, and a micturating cysto-urethrogram carried out.

Technique of Micturating Cysto-urethrography

The patient was asked to empty the bladder and the act of micturition was observed. With aseptic precautions a rubber catheter was passed, and the patency of the external meatus and the ease of passage of the catheter through the urethra were noted. If an obstruction was encountered its distance from the external meatus was measured. If a rubber catheter could not be passed a fine ureteric catheter was tried. The amount of residual urine was recorded. A sterile 25% suspension of barium sulphate was injected slowly until the patient indicated the desire to micturate and then the capacity of the bladder was noted. The patient lay in the supine position with the left leg extended and the right hip joint flexed to an angle of 45 degrees. The pelvis was rotated about 35 degrees to the right, in order to obtain an oblique view of the urethra and base of the bladder. The x-ray tube was rotated 5 degrees towards the patient's head so that the central ray was directed at right angles to the bladder outlet. Micturition was performed in successive stages and three or four exposures were made during the act of micturition.

Whenever an enlarged bladder or urethral obstruction was suspected clinically, or if the residual urine was greater than 30 ml. (1 ounce), a 12% diodone solution was used instead of barium sulphate, in order to avoid reflux of barium into the ureters and renal pelves.

Normal Appearances

Fig. 1 represents diagrammatically the normal outline of the male bladder and urethra during micturating cysto-urethrography. The bladder is smooth in outline but variable in shape; the internal sphincter causes a slight narrowing of the first part of the posterior urethra. Below this the verumontanum, if sufficiently large, may be shown as a spindle-shaped filling defect ½-1 cm. long. At the level of the perineal membrane the urethra may be constricted and this must not be confused with the filling defect of posterior urethral valves or congenital stenosis of the membranous urethra. Beyond this the anterior urethra widens in the bulbous portion and then narrows in the penile segment (Fig. 2). The bulbous urethra may overlap the membranous part if the pelvis is not sufficiently rotated laterally.

FIG. 2.—Micturating cysto-urethrogram of normal boy.

FIG. 3.—Micturating cysto-urethrogram of normal girl.

Fig. 1 also shows the normal outline of the female bladder and urethra; the internal sphincter causes a slight narrowing of the first part of the urethra, and below this there is a slight dilatation of the urethra which tapers towards the external meatus (Fig. 3).

Bladder Capacity

To determine the average bladder capacity, the relationship between bladder capacity and age was examined by fitting a linear equation of bladder capacity on age using 86 children with functional enuresis. The regression equation was:

Bladder capacity in ml. $= 146 + 6 \cdot 1$ (age in years), and the standard deviation from regression was $37 \cdot 7$ ml. (Fig. 4). It should be emphasized that the above equation is limited to an age range of about 5 to 13 years.

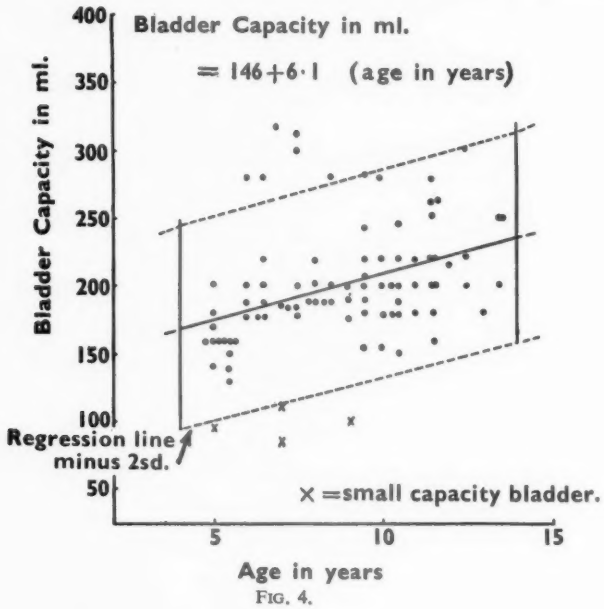

FIG. 4.

Findings

In this series of 135 children with persistent enuresis 84 were boys and 51 girls; the age distribution of each sex is shown in Fig. 5. No organic disease or abnormality of the micturating cysto-urethrogram were found in 43 boys and 31 girls, and in these the enuresis was considered to be of functional origin. Of the 84 boys, 41 were abnormal, 25 with valves of the posterior urethra, one with stenosis of the membranous urethra; nine with a neurogenic disorder of the bladder and one with congenital hypertrophy of the bladder neck. There were two boys with small-capacity bladders, two with severe stenosis of the external meatus and one with a unilateral ureteral reflux without any associated anomaly. Of the 51 girls 20 were abnormal, three with a neurogenic disorder of the bladder and 14 with a wide bladder neck anomaly. There were two girls with small-capacity bladders and one with a unilateral ureteral reflux without any other detectable lesion.

The greater incidence of abnormalities in boys can be mainly attributed to the high proportion of posterior urethral valves which were the commonest disorder encountered in this series. This condition seldom occurs in girls.

Congenital Valves of the Posterior Urethra

According to Young, Frontz and Baldwin (1919) congenital valves of the posterior urethra may be classified anatomically into three main types according to their relation to the verumontanum, as shown in Fig. 6.

Type I shows bifurcated valves springing from the distal end of the verumontanum and passing downwards to the membranous urethra.

Type II (a) shows the valves arising proximal to the verumontanum. (b) The valves arise distal to the verumontanum from the wall of the urethra to form a diaphragm. (c) The valves arise from the verumontanum and pass to the wall of the urethra to form a diaphragm (according to Campbell, 1951).

Type III shows valves which may have up to seven leaves arising from the proximal end of the verumontanum and passing upwards to the bladder neck.

The clinical picture associated with posterior

urethral valves will vary with the degree of obstruction. If this is very marked the newborn infant may present as a case of foetal ascites (Lord, 1953). If the obstruction is less severe the child develops the well-recognized clinical picture of vesical retention with an enlarged palpable bladder, dribbling incontinence, and difficult or hesitant micturition. There is usually evidence of impaired renal function and infection may supervene. The child is often retarded in growth and may even develop renal rickets.

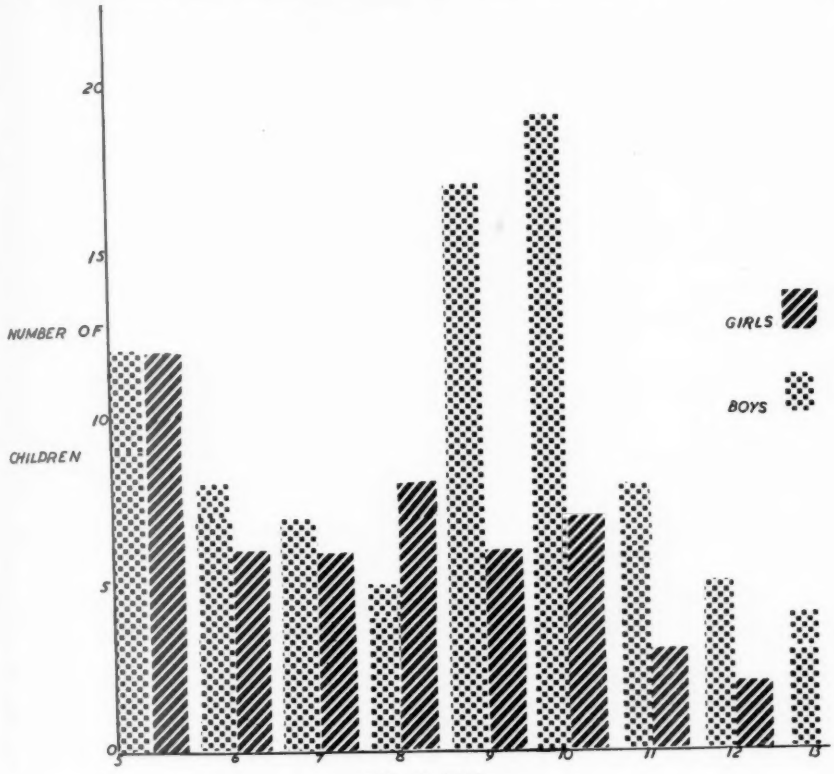

FIG. 5.

In the past many such cases were diagnosed only at necropsy, and although they are more readily recognized now, they are still considered to be rare. Regarding this point, Campbell (1951) states, 'Valvular obstruction of the urethra is not uncommon, it simply fails to be recognized. Most urologists will encounter one or more cases a year; this number represents only a small segment of the total incidence.'

We are in complete agreement with this, but consider that there is still another type of case in which urethral obstruction is unsuspected because of the lack of usual signs and symptoms. The child is usually between 4 and 12 years of age and shows no clinical evidence of enlargement of the bladder, retention of urine or impaired renal function. There is usually a history of frequency since birth and persistent nocturnal enuresis. The child is often continent during the day; we have observed that the enuresis may disappear and be replaced by persistent nocturnal frequency. It is important to realize that this change does not necessarily indicate that the patient is cured.

A review of the literature shows that some cases may remain unrecognized until the third or fourth decade, when infection may supervene and they then present as persistent pyuria, recurrent pyelitis or chronic pyelonephritis. Infection may occur at an

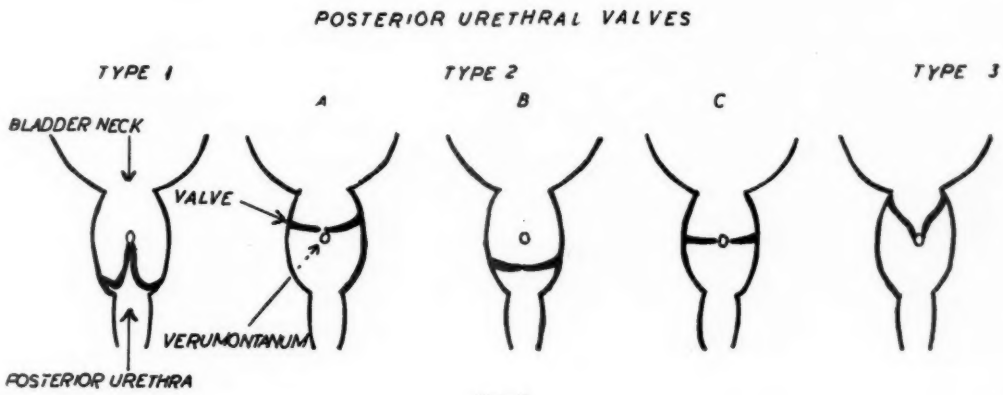

FIG. 6.

earlier age but is not common unless the obstruction is severe or unless it is precipitated by instrumentation. It is possible for these patients to present later with impaired renal function or hypertension and the true nature of the malady may not be appreciated. It is therefore important to recognize and treat the disorder at the enuretic stage before irreparable damage to the urinary system is done.

The clinical picture presented by these 25 children with posterior urethral valves was as follows:

The enuresis was nocturnal in 14, and nocturnal and diurnal in 11. The condition started in infancy in 20, and between 3 and 5 years in the remainder. Frequency was present in 19 and urgency in 12. A history of dribbling was present in five children, and confirmed in three: of these three, two were noticed to strain on micturition. Straining was observed in two others, in one of whom dribbling was noted.

Faecal incontinence was present in five, and was associated with straining on micturition in two of these; the latter feature is important as it must be differentiated from faecal incontinence of neurogenic origin or secondary to chronic constipation.

A family history of enuresis was recorded in eight children, and subnormal intelligence in one. Examination of the urinary tract, which included palpation of the kidneys and bladder and inspection of the external genitalia, was normal, except for one child with hypospadias. The residual urine never exceeded 20 ml., which suggests that at this stage the bladder could be emptied in spite of the obstruction. The bladder capacity varied from 80 ml. to 450 ml. In no case was the urine infected.

FIG. 7.—Micturating cysto-urethrogram showing filling defect due to posterior urethral valves.

FIG. 8.—Micturating cysto-urethrogram showing marked dilatation of posterior urethra proximal to urethral valves.

The diagnosis of a valvular malformation of the posterior urethra was made by micturating cysto-urethrography. In this investigation the valves showed as a constant constriction or filling defect in the posterior urethra (Figs. 7-9). The position of the valves varied, and they were seen in the upper, middle or lower third of the posterior urethra.

In the milder cases there was little dilatation of the posterior urethra above the valves, but as the obstruction became more severe the posterior urethra and internal sphincter widened (Figs. 8 and 9). Trabeculation of the bladder and diverticulum formation occurred and reflux into the ureter followed by hydronephrosis was also seen. In this series the presence and the location of the valves were confirmed by Mr. G. D. F. McFadden at urethroscopy.

Analysis of our cases shows no clear-cut clinical picture, although dribbling or straining on micturition are suggestive signs. It is important to observe the act of micturition to detect these signs, since some of our cases show that the history is unreliable, or the parents are unobservant. If reliance had been placed solely on the presence of dribbling or straining then 21 of our patients

FIG. 9.—Micturating cysto-urethrogram showing marked dilatation of posterior urethra proximal to urethral valves and left ureteral reflux.

would not have been suspected or diagnosed at this early stage of the disease.

The diagnosis of this condition can be made easily by cysto-urethrography and although Campbell (1951) states that such valves may be readily visualized by urethroscopy, such proficiency and skill are exceptional. By the technique of micturating cysto-urethrography not only may the valves be demonstrated but they may be accurately localized and this is of great assistance to the surgeon during urethroscopy and operation.

Neurogenic Disorders of the Bladder

According to Uhle (1913), the internal vesical sphincter is of prime importance in bladder closure in man. In the paralysed bladder with typical funnelling of the bladder neck and urethra, the incontinence is due to dilatation of the internal sphincter and the urethral muscles and not to overflow or paradoxical bladder action. The weakness of the internal sphincter may be compensated by voluntary contraction of the muscles supporting the base of the bladder during the day. At night the muscles relax and incontinence occurs.

In the majority of cases of paralysed bladders there is evidence of neurological disease such as spina bifida with or without meningocoele, disseminated sclerosis, poliomyelitis, spinal cord tumours, etc. There is also a group in which a full neurological examination reveals no abnormality. Nine boys and three girls in our series are considered to be of this type.

The clinical picture revealed that the enuresis was nocturnal and diurnal in all of the children except for one girl with nocturnal enuresis alone. Six boys had been normal for a varying period from $2\frac{1}{2}$ to 9 years of age before enuresis ensued; in the remainder it began in infancy. Urgency was present in 10 children and frequency in eight; a history of dribbling was obtained in five and observed in three. Occasional faecal incontinence was present in six children and four had poor anal tone. A family history of enuresis was obtained from one child, another was mentally subnormal. There was no detectable clinical abnormality, motor or sensory, of the central nervous system in any case. The residual urine varied from 0 to 30 ml. and the bladder capacity from 120 to 960 ml. The urine was infected in two of these children. X-ray examination of the lumbar and sacral spine showed spina bifida in 10 of these children with splitting of the arch of the fifth lumbar vertebra in one boy and of the first sacral vertebra in eight boys and one girl.

Micturating cysto-urethrography revealed the characteristic smooth funnelling of the bladder outlet and urethra. In some cases, the bladder was greatly increased in capacity up to 960 ml.; in others the bladder was contracted and trabeculated, and in one of these bilateral urethral reflux was observed towards the end of micturition (Figs. 10-12).

FIG. 10.—Micturating cysto-urethrogram showing enlarged bladder with paralytic funnelling of bladder neck and dilatation of posterior urethra.

FIG. 11.—Micturating cysto-urethrogram showing paralytic bladder neck and bilateral ureteral reflux.

The marked dilatation of the posterior urethra and the non-functioning internal vesical sphincter were confirmed at urethroscopy and cystoscopy by Mr. McFadden.

Burns (1917) was the first to describe the characteristic funnelling of the bladder neck which is associated with bladder paralysis. He showed that the degree of funnelling depended on the amount of bladder distension and that it might become fixed and very wide in the contracted bladder with almost complete closure of the urethra at the external sphincter. However, in some of our patients the dilatation of the urethra was so gross that it extended beyond the external sphincter.

The examination of the central nervous system of these 12 children was normal except for poor anal tone in three, and the presence of a mild degree of spina bifida in 10. According to Riches (1944), although there may be only a mild degree of spina bifida occulta, the constant accompaniment of the typical cystoscopic picture leaves no doubt that the urinary symptoms are produced by it. Also it is noteworthy that the enuresis in five of the boys did not begin until after 5 years of age. Ingraham and Swan (1943) have shown that as a child grows tension may be placed on the spinal cord by a lipoma or fibrous tissue in association with spina bifida because of the more rapid growth of the vertebral canal compared with the spinal cord. This usually occurs between 6 and 10 years of age. About 50% of their cases of enuresis were cured by laminectomy, but those cases with only a mild degree of spina bifida did not improve following operation. However, Karlin (1935) states that 'spina bifida occulta can be considered as an organic basis for enuresis only in those cases which show an extensive involvement of the vertebrae in the lumbo-sacral region and also cases showing neurological signs'. The relationship between neurogenic disorder of the bladder and spina bifida requires further investigation.

From our series it is evident that a late onset of enuresis of a diurnal and nocturnal character, associated with urgency and frequency, dribbling without straining and occasional faecal incontinence, is suggestive of a neurogenic disorder of the bladder. However, this combination of symptoms and signs may also be observed in functional cases, and therefore micturating cysto-urethrography is essential in the diagnosis of this type of case especially as there are no abnormal neurological signs. The micturating cysto-urethrogram also provides a permanent record of the abnormality and this greatly facilitates the surgeon in the planning of operative treatment.

Wide Bladder Neck Anomaly in Girls

In addition to the three girls already described with a neurogenic disorder of the bladder, micturating cysto-urethrography revealed an abnormally wide bladder neck in a further 14 girls. This radiological finding, although somewhat variable, was

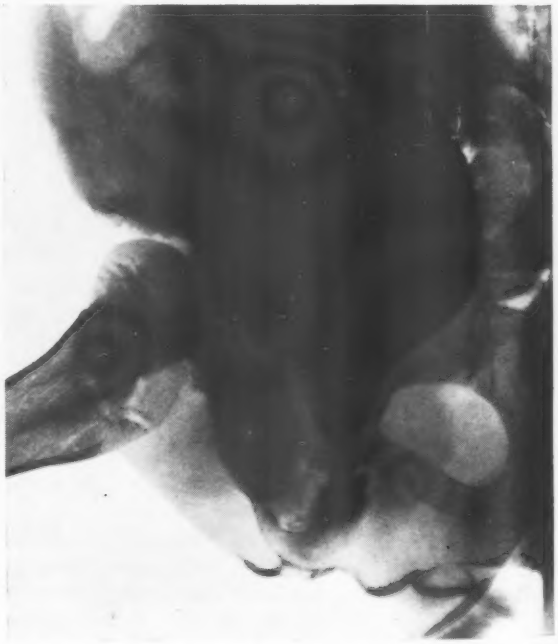

FIG. 12.—Micturating cysto-urethrogram of girl, showing paralytic funnelling of bladder neck.

distinct from the smooth funnelling characteristic of a paralysed bladder neck.

The enuresis was nocturnal and diurnal in 11 and nocturnal in three. The condition began in infancy in seven and between 2 and 9 years of age in seven. Frequency and urgency were present in all but one. Only one child had occasional faecal incontinence, one was mentally subnormal and there was a family history of enuresis in four. The bladder capacity varied from 160 to 220 ml. and in four children there was a coliform infection of the urine. Rectal examination revealed that the anal tone was normal in all cases. Radiographs of the lumbar and sacral spines showed splitting of the arch of the first sacral vertebra in seven. However, three important points were noted: (1) Five girls gave a history of dribbling without straining. (2) One child had stress incontinence and her mother and grandmother suffered from the same disability from childhood. (3) No neurological disorder could be detected clinically.

Micturating cysto-urethrography demonstrated marked widening of the internal sphincter and upper part of the urethra. The urethra became normal in size at the external meatus and thus gave rise to the appearance of a spinning-top stuck to the base of the bladder (Figs. 13-14). A ureteral reflux was demonstrated in one patient at the beginning and end of micturition.

The cause of the wide bladder neck in girls is difficult to determine and there seem to be several possible explanations: (*a*) Neurogenic disorder of the bladder, (*b*) simple atony of the internal sphincter, (*c*) dilatation of the sphincter as a result of an infection or an obstruction in the urethra. The micturating cysto-urethrogram did not show the typical funnelling of a paralytic bladder and there were no abnormal neurological signs.

FIG. 13.—Micturating cysto-urethrogram showing wide bladder neck anomaly.

FIG. 14.—Micturating cysto-urethrogram showing wide bladder neck anomaly with unilateral ureteral reflux.

Campbell (1951) has demonstrated that children with chorea frequently develop a large atonic bladder; micturating cysto-urethrography undertaken in five children with chorea showed that the bladder capacity was increased above the normal average for their age, but there was no evidence of widening of the internal sphincter.

The most likely cause of an obstruction of the urethra, when foreign bodies and calculi are excluded, is either meatal stenosis or mucosal valves which have been described by Addison (1932). Difficulty was encountered on catheterization for cysto-urethrography in only one girl. The obstruction was considered to be due to marked meatal stenosis: this was confirmed and relieved at operation.

Addison (1932) in his description showed that the valves occur close to the external meatus. If this is the case then these valves may be very difficult to visualize by urethroscopy. In our cases which have been subjected to operation a catheter was passed down the urethra from the bladder without encountering an obstruction, except in the patient with meatal stenosis.

It is well known that chronic inflammation of the bladder may give rise to dilatation and impaired function of the uretero-vesical sphincters. It seems reasonable to assume that a similar dilatation may occur at the internal vesical sphincter. Four of our cases had a urinary infection, and although the infection responded to treatment enuresis persisted. At urethroscopic examination before operation none of the children with a wide bladder-neck anomaly showed signs of inflammation around the internal sphincter or urethra, and therefore it seems unlikely that infection was responsible for the dilatation.

In a study of enuretic children, Campbell (1934) found that urethro-trigonitis was the commonest lesion in girls and often occurred in boys. We have found that in children with inflammation around the bladder neck, micturating cysto-urethrography is of no value in detecting the condition. However, if a chronic cystitis is present, fuzziness or a moth-eaten appearance of the cystographic outline is frequently seen.

Finally, the clinical picture was not helpful in distinguishing this group from children with functional enuresis, although dribbling without straining and the presence of stress incontinence were suggestive. It is therefore impossible to separate this group from the functional cases without cysto-urethrography.

Small Capacity Bladder

Vesical spasm is common in childhood and may be attributed to reflex causes such as vesical or urethral inflammation, calculi, or rectal disturbance such as anal fissure.

There is, however, a small group of children who have a very limited bladder capacity in whom no such cause can be detected. This condition resembles the high tension bladder of infancy and results in frequency, urgency, precipitate micturition and enuresis. Two boys and two girls were considered to be of this type.

The clinical picture revealed that the enuresis was nocturnal in the boys and nocturnal and diurnal in the girls. Three started in infancy and one boy at 3 years of age. Frequency was present in two boys and one girl, and urgency in one boy and two girls. One of the girls was mentally subnormal and the other had a urinary infection.

Micturating cysto-urethrography demonstrated on repeated examination that the bladder capacities fell below the normal average for their ages (Fig. 4). All of these children were typical in showing great discomfort when the bladder reached its maximum capacity which varied from 90 to 120 ml. This was followed by explosive or uncontrollable micturition. The cysto-urethrogram showed a small bladder with a smooth outline and a normal urethra.

As no local cause could be found for the condition it was probably due to a failure of physiological development. The cysto-urethrogram was normal, which distinguishes this condition from the hypertonic spastic bladder where there is a constriction at the internal sphincter and frequently bladder trabeculation.

Meatal Stenosis

Stenosis of the external meatus may be congenital or acquired and the degree of obstruction is variable. If it is slight, the patient may complain of dysuria and pass urine in a fine or intermittent stream. If severe, fatal retention may occur and this has been recorded by Higgins, Williams and Nash (1951). Four boys and one girl were found to have this disorder. The girl had an associated wide bladder-neck anomaly and was considered above. One of the boys with a pinhole meatus and a second degree hypospadias was subsequently found to have hypertrophy of the internal vesical sphincter and this will be discussed below. Another boy with a valvular anomaly has been included with the 25 cases of posterior urethral valves. Two boys remain to be considered.

The clinical picture revealed that the enuresis was nocturnal in one and nocturnal and diurnal in the other. One complained of frequency and urgency, but neither gave a history of dysuria. The symptoms were present from infancy in both and in one case the symptoms developed after circumcision. In both cases the stenosis was not seen on inspection.

During micturating cysto-urethrography it was found that a rubber catheter could not be passed into the urethra and a fine ureteric catheter was used instead. When micturition began the urine was expelled in a fine stream.

The diagnosis of meatal stenosis is usually made by inspection, but in these two boys the condition was not evident until a rubber catheter was used. Stockwell and Smith (1940) described 23 cases of meatal stenosis in a series of 100 children with enuresis but they thought that in only three of these it was the primary cause. One of our patients was cured by meatotomy, but the other is unchanged.

Congenital Stenosis of the Membranous Urethra

This is an uncommon condition and in the absence of a history of trauma or infection it is likely to be congenital in origin. One boy showed this malformation. His enuresis, which started in

infancy, was nocturnal and diurnal. Frequency and urgency were present and there was a history of straining during micturition which was associated with occasional faecal incontinence.

Before micturating cysto-urethrography, passage of the rubber catheter was prevented by an obstruction 7·5 cm. from the external meatus. A fine ureteric catheter was passed successfully and the cysto-urethrogram showed marked dilatation of the posterior urethra and internal sphincter proximal to the obstruction. A large diverticulum was present on the left side of the bladder (Fig. 15).

Congenital Hypertrophy of the Vesical Outlet

A review of the literature has shown that some of these cases, like those of valvular anomalies, may remain unrecognized until the second or third decade. Congenital hypertrophy of the vesical outlet may be associated with meatal stenosis or stenosis at the uretero-vesical junction. Campbell (1930) drew attention to the similarity of this condition and congenital hypertrophy of the pylorus. One of the boys showed this anomaly which was associated with pinhole meatal stenosis and second degree hypospadias.

His enuresis began in infancy and was nocturnal and diurnal. Marked frequency was present and the child complained of difficulty in passing urine.

The pinhole meatus was easily recognized but there was no evidence of distension of the penile urethra behind the obstruction and it was thought there must be an obstruction higher up. Micturating cysto-urethrography showed that the supracollicular portion of the urethra was elongated

FIG. 15.—Micturating cysto-urethrogram showing marked dilatation of posterior urethra proximal to stenosis of membranous urethra. Note bladder diverticulum.

FIG. 16.—Micturating cysto-urethrogram showing narrowing of posterior urethra due to congenital hypertrophy of bladder neck. Note dilatation of urethra proximal to the meatal stenosis and the fine ejection stream.

and compressed (Fig. 16). Towards the end of micturition a left ureteral reflux was observed. At operation the hypertrophied sphincter was palpated rectally when a urethral dilator was inserted. Following operative treatment the enuresis disappeared.

Congenital hypertrophy and congenital contracture of the internal sphincter are probably variations of the same condition. Brodny and Robins (1944) have shown in the latter condition that the internal sphincter is shortened and constricted and the bladder base flattened. In congenital hypertrophy of the vesical outlet the internal sphincter forms a collar-like structure which projects into the floor of the bladder, giving rise to a concave filling defect. It compresses and elongates the urethra at this level.

Uretero-Vesical Reflux

Bell (1812) demonstrated that the intramural part of the ureter was compressed and had a more competent valvular action when the bladder was distended than when it was contracted and the ureter was less oblique. In 1925 Graves and Davidoff showed by experiments on cats, dogs and rabbits that ureteral reflux depends primarily upon the sustained tonus of the bladder; that is, reflux never occurs when the active sustained contraction is lack-

ing, e.g. in a paralytic bladder. Young *et al.* (1919) observed in some of their cases of posterior urethral valves and in other reported cases that when the ureters communicate with the bladder through a large orifice the bladder was usually contracted. Riches (1943) recorded in his cases with neurogenic disorders of the bladder that the ureteral reflux occurs towards the end of micturition.

In this series, five children showed radiological evidence of ureteral reflux towards the end of micturition. The reflux was not found when the bladder was distended. A bilateral ureteral reflux was associated with a neurogenic disorder of the bladder in one case. Two patients with unilateral reflux were seen in association with valvular anomaly of the posterior urethra. The child with congenital hypertrophy of the bladder neck was found to have a unilateral ureteral reflux. One of the girls with a wide bladder-neck anomaly showed a unilateral ureteral reflux throughout micturition. It may be that the uretero-vesical valve was dilated by a similar mechanism as the internal vesical sphincter.

In another boy and girl no abnormality was found to account for the reflux; although the girl had a urinary infection this was not thought to be the primary cause. The significance of vesico-ureteral reflux is debatable in these two cases. Campbell (1951) states that he has never observed it in the absence of demonstrable urological disease. However, Gibson (1949) recorded two cases in a series of 43 children in whom the urinary tract was apparently normal, but we note that cystoscopy was not undertaken.

Functional Enuresis

As no organic disease or abnormality of the micturating cysto-urethrogram were found in 43 boys and 31 girls their enuresis was considered to be of functional origin. However, five of these

TABLE
SIGNS AND SYMPTOMS OF 135 CHILDREN WITH PERSISTENT ENURESIS

Type of Case	Functional Enuresis		Neurogenic Disorder of the Bladder		Small Capacity Bladder		Posterior Urethral Valves	Wide Bladder Neck Anomaly	Stenosis of Membranous Urethra	Meatal Stenosis	Congenital Hypertrophy of Vesical Neck	Unilateral Ureteral Reflux	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Boys	Boys	Boys	Girls
Number of cases	43	31	9	3	2	2	25	14	1	2	1	1	1
With onset in infancy	34	20	3	3	1	2	20	7	1	2	1	—	1
Nocturnal enuresis	32	14	—	1	2	—	14	3	—	1	—	1	1
Nocturnal and diurnal	11	17	9	2	—	2	11	11	1	1	1	—	—
Frequency ..	14	16	6	2	2	1	19	13	1	1	1	—	1
Urgency	14	19	8	2	1	2	12	13	1	1	—	—	1
History of dribbling ..	2	2	5	—	—	—	5	5	1	1	1	—	—
Straining ..	—	—	—	—	—	—	2	—	1	—	—	—	—
Faecal Incontinence	6	2	6	—	—	—	5	1	1	—	1	—	—
Family history of enuresis	20	9	1	—	—	—	8	4	1	—	—	1	—
Subnormal I.Q.	1	4	1	—	—	1	1	1	—	—	—	—	—
Observed dribbling ..	—	—	3	—	—	—	4	—	1	—	1	—	—
Observed straining	—	—	—	—	—	—	4	—	1	—	—	—	—
Poor anal tone ..	3	2	3	1	—	—	1	—	—	—	1	—	—
Urinary infection	—	5	2	—	—	1	—	4	—	—	—	—	1

children were found to have a urinary infection; in four the urine contained no pus cells but coliform organisms were present; in the other there was a pyuria due to *B. proteus*. Although the infection responded to treatment in all, the enuresis persisted.

When this investigation was initiated the relevant signs and symptoms were recorded as it was hoped that separate clinical patterns would be determined for each aetiological group. These are recorded in the table, and from this it can be seen that the clinical picture was so varied in the functional group that it could not be distinguished from the organic conditions.

Summary and Conclusion

One hundred and thirty-five children with persistent enuresis were investigated by micturating cysto-urethrography.

In 43 boys and 31 girls the enuresis was considered to be of functional origin.

In 41 boys and 20 girls this procedure revealed abnormalities of the urinary tract. These included valves of the posterior urethra (25), neurogenic disorders of the bladder (12), wide bladder-neck anomaly (14), small capacity bladder (four), meatal stenosis (two), ureteral reflux (2), stenosis of the membranous urethra (one) and congenital hypertrophy of the vesical neck (one).

The symptoms and signs of the organic disorders did not distinguish them from the functional enuretics.

The radiological technique is simple enough to be undertaken in any radiographic department and it causes no more disturbance to the child then catheterization.

It is our opinion that micturating cysto-urethrography is an essential investigation for the detection of organic disorders of the urinary tract in children with persistent enuresis.

We acknowledge with gratitude the advice and encouragement of Professor F. M. B. Allen, and the skill and experience of Mr. G. D. F. McFadden who performed the urological examinations.

We wish to thank the medical, radiological and nursing staffs of the Royal Belfast Hospital for Sick Children and the Ulster Hospital for Children and Women for their invaluable co-operation.

References

Addison, O. (1932). *Archives of Disease in Childhood*, **7**, 25.
Bell, C. (1812). *Med.-Chir. Trans. Lond.*, **3**, 171.
Brodny, M. L. and Robins, S. A. (1944). *J. Amer. med. Ass.*, **126**, 1000.
Burns, J. E. (1917). *Surg. Gynec. Obstet.*, **24**, 659.
Campbell, M. F. (1930). *J. Amer. med. Ass.*, **94**, 1373.
—— (1934). *N.Y.St. J. Med.*, **34**, 190.
—— (1951). *Clinical Pediatric Urology*. Philadelphia.
Cohen, D. L. (1947). *J. Urol., Baltimore*. **57**, 331.
Despert, J. L. (1944). *Psychomat. Med.*, **6**, 294.
Gibson, H. M. (1949). *J. Urol., Baltimore*, **62**, 40.
Graves, R. C. and Davidoff, L. M. (1925). *Ibid.*, **14**, 1.
Higgins, T. T., Williams, D. I. and Nash, D. F. E. (1951). *The Urology of Childhood*. London.
Ingraham, F. D. and Swan, H. (1943). *New Engl. J. Med.*, **228**, 559.
Karlin, I. W. (1935). *Amer. J. Dis. Child.*, **49**, 125.
Lord, J. M. (1953). *Archives of Disease in Childhood*, **28**, 398.
Riches, E. W. (1943). *Brit. J. Surg.*, **31**, 135.
—— (1944). *Proc. roy. Soc. Med.*, **37**, 77.
Sheldon, W. (1944). *Ibid.*, **37**, 348.
Stockwell, L. and Smith, C. K. (1940). *Amer. J. Dis. Child.*, **59**, 1013.
Thorne, F. C. (1944). *Amer. J. Psychiat.*, **100**, 686.
Uhle, A. A. (1913). *Trans. Amer. Ass. gen.-urin. Surg.*, **8**, 303.
Young, H. H. Frontz, W. A. and Baldwin, J. C. (1919). *J. Urol., Baltimore*, **3**, 289.

BOOK REVIEWS

Congenital Syphilis. By DAVID NABARRO. (Pp. 470; 95 figures. 50s.) London: Edward Arnold. 1954.

Forty-nine years after the appearance of his first book and forty-seven years after the publication of his second, Dr. Nabarro's long awaited third book *Congenital Syphilis* has at last appeared. It will receive a warm welcome from all students of congenital syphilis and will be an eye-opener for all those who have grown up in the penicillin era.

Dr. Nabarro's experience was gained mainly as Director of the Venereal Diseases Clinic at The Hospital for Sick Children, Great Ormond Street, from 1917 to 1938. During this period some 1,000 cases of congenital syphilis were treated. Although this may not be a great number compared with what some other countries can assemble, it must be remembered that the staff of such a clinic was kept at a minimum and the Director of the Clinic thus would come in intimate and continuing contact with his patients. Against the background of this experience the story of congenital syphilis is told in all its aspects from the history, through the symptomatology, which naturally occupies the major part of the book, to treatment, while there is a short consideration of acquired syphilis in childhood.

To the many of us who have never seen a gumma and possibly but two or three cases of congenital syphilis in the last 10 years, the breadth of Dr. Nabarro's subject will come as a stimulating reminder of the advances in prophylactic medicine in our time, and the older generation, versed in the different aspects of congenital syphilis, may well feel some nostalgia for the diagnostic fields that were; while the newer generation, obsessed with spikes, waves and milli-equivalents, may breathe a sigh of relief that here at least is one field on which they may pardonably remain inexpert.

Some say that syphilis, and particularly in its congenital form, is a dying disease; if it is then Dr. Nabarro's book will become a historical document in the English literature. He, however, expresses some doubt concerning the certainty of the rapid eradication of congenital syphilis in this country. For this reason he recommends that in spite of our apparent success in treating syphilis no treacherous feeling of smugness should be permitted, venereal diseases should continue to be properly taught in the undergraduate and postgraduate teaching hospitals, and that a proper look-out for syphilis should be maintained by clinicians.

With such a wealth of clinical material it is not surprising that Dr. Nabarro has developed certain interests within his subject and thus we find a very full consideration of congenital neurosyphilis as well as the relation of congenital syphilis to sundry other diseases such as herpes and parotitis. But the major value of the book is that it forms a historical record and will for a long time remain a yardstick whereby to measure the improvement in results of treatment of a disease which, mercifully, none of us in this country is ever likely to see as much as did Dr. Nabarro.

Endocrinology in Clinical Practice. Edited by GILBERT S. GORDAN and H. LISSER. (Pp. 407; 90 figures. 80s.; $10.50.) Chicago: The Year Book Publishers, Inc.; distributed in the U.K. by Interscience Publishers Ltd. 1953.

Into this relatively slender volume is packed a compound of lectures which first made up a 1952 postgraduate course in endocrinology and metabolic disease presented by the University of California Medical School. All but two of an imposing array of 30 participants are members of its teaching staff. As a chronicle of their outlook it has a significant place for the endocrinological devotee. But what of the editors' claim to serve primarily the general physician, affording him a practical clinical guide to specialized territory in the throes of revolutionary expansion?

Even allowing for abrupt fluctuations in standards inevitable in a book of this make-up, one still feels that this admirable objective is too often overlain by the heavy therapeutic bias which has for so long plagued endocrinological progress. Too often, the elusive pearls of clinical guidance are also usurped by unwieldy classifications. In thus disposing of diagnosis in amenorrhoea, an exhortation to systemic thought is followed by shackling it to a classification taking up two pages. The injunction that diagnostic exclusion may begin either at top or bottom of this list does little to retrieve the doctor from a weary sojourn somewhere between pregnancy and true hermaphroditism. The classification introducing sex precocity even regenerates ancient confusions. For example, precocity is dubbed as 'true' whether deriving from pineal, gonadal or adrenal tumours. Why obscure the elementary diagnostic distinction which depends upon the development of a true precocious puberty embodying gonadal maturation only in 'cerebral' cases?

Challenged by the editor's invitation to paediatricians, we can at most concede that its paediatric perspective is less skimped than is usual in most medical textbooks. We could expect to be less often disappointed when seeking paediatric details of presentation and management. Even failure in growth is viewed largely from the standpoint of adolescence. Exception may also be taken

to Professor Lisser's sweeping advocacy of early androgenization for the small 'delayed adolescent'. Surely a standardized pattern of strapping androgenic muscularity, with appropriated emotional drives, cannot be a compelling need for all small boys lagging behind pubertal schedules at 12 to 13 years. We also remain worried by the advice that even where the bone-age is normal, quite apart from basal metabolic rates and cholesterol levels, that 'sluggishness, poor concentration, dry straight hair' may, when linked to 'mild growth retardation' and other such non-specific criteria, justify a plunge into endocrine therapy, this time with thyroid of course. We already see thyroid too often stubbornly persisted with for years in vain wait for the 'gratifying improvement' offered here as the yardstick of diagnostic response.

The paediatrician is already better served in books entirely dedicated to his needs in this field. Nevertheless, there is much of lively interest to any physician in contributions of the calibre of that on calcium metabolism, or in the initial sections enunciating general principles. It is here that we especially welcome Lisser's forthright call for a revival of basic clinical skills in balanced clinical approach to the patient as a whole, and Escamilla's portrayal, in frank perspective, of the secondary role and fallibility therein of laboratory aids. These strike healthy reassuring chords in harmony with fundamental traditions of clinical teaching, still unashamedly nurtured here and there.

The Surgery of Infancy and Childhood. By ROBERT E. GROSS. (Pp. 1000; 567 figures. 80s.) Philadelphia and London: W. B. Saunders Company. 1953.

This beautifully produced book will very soon become a standard reference for all surgeons and paediatricians. It brings up to date the classic work of Ladd and Gross and at the same time widens its scope to include all conditions in childhood requiring surgical treatment.

In these days of anatomically limited specialization how refreshing it is to read a book written by one surgeon dealing in a masterly way with widely different conditions. A surgeon with the experience of Dr. Gross can afford to be dogmatic about the worth of different operations, and therein lies the value of this book. Descriptions of out-of-date methods have been avoided and the essentials compressed into what is still a very readable volume.

The illustrations are numerous and of a very high standard. The steps of the operative procedures are very clearly shown, and perhaps make the more complicated ones look too easy; surgeons with very little experience and imperfect technique might be encouraged to undertake operations beyond their scope.

The excellent chapter on pre-and post-operative treatment of young infants will be of great interest to paediatricians who care for such cases. The advice given is detailed and full of good illustrations on practical procedures.

Perhaps the greatest value of this excellent book will be for reference by those who are called to deal with a child with some rare condition amenable to surgery with which they are unacquainted.

Pediatric Gynecology. By GOODRICH C. SCHAUFFLER. Third edition. (Pp. 318; 76 illustrations. 57s. or $7.50.) Published by the Year Book Publishers, Chicago; distributed in Great Britain by Interscience Publishers. 1953.

It is a truism that specialities automatically divide themselves into sub-specialities and at first sight this work of Dr. Schauffler would appear to be one of the minuter of such sub-specialities, whether of paediatrics or gynaecology being debatable; but by the time this book has been read little doubt is left that the scope of the subject almost warrants the creation of a new speciality. The description of methods of investigation of the female genitalia, treatment of vaginitis, disorders encountered during adolescence, the surgery of the pelvic contents, with which are included some considerations of the lower gut and rectum, and medico-legal problems combine with short accounts of enuresis and such subjects as Wilms' tumour to create a not inconsiderable subject matter. In some of the more specialized aspects of his subject Dr. Schauffler has enlisted the help of collaborators but throughout the book it is clear that these have been prepared to subordinate their individualities to that of the senior author; the result is a homogeneous whole.

Most of the subject matter is based on what is evidently a wide personal experience and there is little of it with which the average British paediatrician will disagree except in such minor points as the treatment of enuresis where such disagreement is only right and traditional. Particularly helpful are the methods of clinical investigation and the treatment of vulvovaginitis, while the illustrations are at all times clear and contributory.

In spite of its apparently limited appeal this book can be commended with confidence not only to paediatricians but to all clinicians whose work involves the treatment of little girls' pelvic organs, and the reader will find a fairly definite but not unduly dogmatic view expressed on almost any problem in this field on which he seeks guidance.

Natal Day Deaths. By HERMAN N. BUNDESEN. (Pp. 44. No price.) Chicago: Office of the President of the Board of Health. October 12, 1953.

Dr. Bundesen is President of the Board of Health of Chicago and well known for his organization of the care of premature infants in that city. In the present pamphlet —an enlarged version of a communication read before the Section of Paediatrics of the American Medical Association, at its one hundred and second annual session—he attacks a 'long neglected field of infant mortality', namely those deaths among infants of lower birth weight in the early days of life. His thesis is that all concerned must concentrate on the fact that more deaths occur in the first three days of life than in the whole of the rest of the first year. This is an elaboration of what Clement Smith has called 'the valley of the shadow of birth', and it offers great scope. In particular what Dr. Bundesen calls 'abnormal pulmonary ventilation' requires better efforts to prevent a fatal issue.

Anoxia of the Newborn Infant. A Symposium. (Pp. 230; illustrated. 27s. 6d.) Oxford: Blackwell Scientific Publications. 1953.

As stated in the foreword, this monograph is the record of the papers which were delivered and the discussions that took place at the symposium on 'Anoxia of the Newborn Infant', held in London in October, 1951, under the auspices of the Council for International Organizations of Medical Sciences. All the 17 contributors are internationally recognized experts in their own fields, hence the papers are of a high standard, if at times somewhat unrelated to one another.

The papers have been collected under the following headings: clinical, pathological, biochemical, physiological and therapeutic, and in all of them the principal theme is respiration in the newborn. The embryology and evolution of the lungs and 'the hyaline membrane' are discussed and illustrated fully, as is the mode of onset of rhythmical breathing in the premature infant.

This book will be of interest and value both to the obstetrician and the paediatrician, but the title of anoxia of the newborn infant is misleading. Anoxia and its effects are only briefly mentioned.

Diagnosis of Acute Abdominal Pain. By WILLIAM REQUARTH; with Foreword by Warren H. Cole. (Pp. 243; 79 illustrations. 38s.; $5.00.) Chicago: The Year Book Publishers. Distributed in Great Britain by Interscience Publishers Ltd. 1953.

In his foreword Dr. Warren Cole writes, 'Although this book will find its greatest application to the young surgeon, it is nevertheless so practical and complete for its size that it will be found extremely useful to anyone doing emergency work involving the abdomen.' Although the main interest of readers of the *Archives* and of the reviewer is, naturally, in the chapter on the acute abdominal lesions of infancy, it is impossible to limit the review to this chapter, good as it is. The book is obviously written by a practical surgeon who has been successful in writing clearly and concisely on a difficult subject. The importance of clinical examination is stressed throughout and it is refreshing to read that 'physicians tend to place too much reliance on laboratory findings, and to utilize them as a less bothersome road to correct diagnosis than their own eyes and ears'. The reviewer has no hesitation in endorsing the opinion of Dr. Warren Cole which is quoted above.

Clinical Management of Behavior Disorders in Children. By HARRY BAKWIN and RUTH MORRIS BAKWIN. (Pp. 495 ; 14 figures. 50s.) London: W. B. Saunders. 1953.

This book, written by two paediatricians, owes and acknowledges a debt to their psychiatric colleagues. Nevertheless, it is written for all who have the ordinary day-to-day care of emotionally disturbed children, and a quotation on the front page, from a *Lancet* editorial, sets the tone. 'Nature's methods, perfected over millions of centuries, are always purposeful and nearly always right.'

In the authors' introduction they state their aim as seeking 'to bring together from many sources, and from the clinical experience of the authors, the best available information on the psychologic aspects of child care'. This is clearly a difficult task to achieve; no authors so experienced as these can fail to have certain preferences, and possibly a few prejudices. Because they give a large part of their book to summarizing the work of others, it necessarily becomes a work of reference, almost a dictionary, rather than a critical examination and selection of the views which they themselves put forward. While it may not satisfy those who wish to discover a deeper cause for the many manifestations of psychosomatic disorder in childhood, it cannot fail to prove itself an enormously useful book to any worker in this field who wants to know what work has been done, when, where and by whom.

The general arrangement of the book is extremely clear and logical and allows for quick reference to be made to the original papers, even when these deal only with a subdivision of the subject. In a sense it is not a profound book, but it avoids extreme didactic certainty and method, and certainly paves the way, most acceptably, for wider reading.

Deuxième Congrès International d'Hygiène et de Médicine Scolaire, Lyon, 9, 10, 11 and 12 July, 1952. (Pp. 504; illustrated. Fr. Frs. 3,000-) Paris: G. Doin & Cie. 1953.

This publication is the collection of the 68 papers read at the Conference held in Lyons in July, 1952. These fall into three main groups. The first deals with the problem of tuberculosis in schools, including the tracking down of cases by mass radiography, the routine use of the Mantoux test together with the interpretation of the reading of the results, the importance of examining teachers, and the results of B.C.G. vaccination. The second group of papers is concerned with the schooling of backward children, and several of the authors stress the importance of deafness or partial deafness as a cause and deal with the problem of the education of such pupils. The final, miscellaneous, section covers school hygiene—canteens, holidays, open-air schools, oxyuriasis and ringworm infections.

This book should be of interest to all who are in contact with the problems of school health and hygiene. The papers are uniformly short and well written, and the results and conclusions are simply presented.